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(19) (CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Hydroxylated Inhibitors of HIV Reverse Transcriptase

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(57) 33 Claims

Notice: The specification contained herein as filed

Canada

CCA 3254 (10-89) 41

155/RDM80
156/RDM81

2053512

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18212Y

10 TITLE OF THE INVENTION

HYDROXYLATED INHIBITORS OF HIV REVERSE TRANSCRIPTASE

ABSTRACT OF THE DISCLOSURE

Novel biotransformed or synthetic hydroxy
15 pyridinones inhibit HIV reverse transcriptase, and
are useful in the prevention or treatment of
infection by HIV and the treatment of AIDS, either as
compounds, pharmaceutically acceptable salts (where
appropriate), pharmaceutical composition ingredients,
20 whether or not in combination with other antivirals,
anti-infectives, immunomodulators, antibiotics or
vaccines. Methods of treating AIDS and methods of
preventing or treating infection by HIV are also
described.

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- 1 -

18212 Y

10 TITLE OF THE INVENTION

HYDROXYLATED INHIBITORS OF HIV REVERSE TRANSCRIPTASE

This application is a continuation-in-part of U.S.S.N. 07/712,326, filed June 7, 1991, which is a 15 continuation-in-part of U.S.S.N. 07/599,968, filed October 18, 1990. This application is related to Merck case 18122, 18122IA, 18122IB, 18131, 18131IA, 18132, 18317, 18376, 18377, 18379, 18463, 18464 and 18465.

The present invention is concerned with 20 compounds which inhibit the reverse transcriptase encoded by human immunodeficiency virus (HIV). The compounds are of value in the prevention of infection by HIV, the treatment of infection by HIV and the treatment of the resulting acquired immune deficiency

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syndrome (AIDS). The present invention also relates to pharmaceutical compositions containing the compounds and to a method of use of the present compounds with or without other agents for the 5 treatment of AIDS & viral infection by HIV.

BACKGROUND OF THE INVENTION

A retrovirus designated human immunodeficiency virus (HIV) is the etiological agent of the 10 complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous system. This virus was previously known as LAV, HTLV-III, or ARV. A common feature of 15 retrovirus replication is reverse transcription of the RNA genome by a virally encoded reverse transcriptase to generate DNA copies of HIV sequences, a required step in viral replication. It is known that some compounds are reverse 20 transcriptase inhibitors and are effective agents in the treatment of AIDS and similar diseases, e.g., azidothymidine or AZT.

Nucleotide sequencing of HIV shows the presence of a pol gene in one open reading frame 25 [Ratner, L. et al., Nature, 313, 277(1985)]. Amino acid sequence homology provides evidence that the pol sequence encodes reverse transcriptase, an endonuclease and an HIV protease [Toh, H. et al., EMBO J. 4, 1267 (1985); Power, M.D. et al., Science, 30 231, 1567 (1986); Pearl, L.H. et al., Nature 329, 351 (1987)].

Applicants demonstrate that the compounds of this invention are inhibitors of HIV reverse transcriptase. The inhibition is very specific, since there is little or no inhibition of the reverse transcriptases of AMV, MMLV or SIV. Further, the compounds of the present invention do not require bio-activation to be effective. They are also generally more potent than AZT.

Applicants have discovered that hydroxylation in certain positions in the pyridinone ring confer the simultaneous advantages of compounds that are both metabolic products and potent inhibitors of HIV reverse transcriptase. Some of the lead compounds of the present invention are biotransformations of an HIV reverse transcriptase inhibitor L-696,040. The biotransforming microorganism is Actinoplanacete sp. (Merck Culture Collection MA 6559) ATCC No. 53771. Applicants have now also synthesized a variety of analogs.

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BRIEF DESCRIPTION OF THE INVENTION

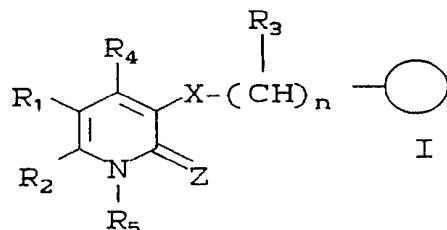
Compounds as herein defined are disclosed. These compounds are useful in the inhibition of HIV reverse transcriptase, the prevention of infection by HIV, the treatment of infection by HIV and in the treatment of AIDS and/or ARC, either as compounds, pharmaceutically acceptable salts (when appropriate), pharmaceutical composition ingredients, whether or not in combination with other antivirals, anti-infectives, immunomodulators, antibiotics or

vaccines. Methods of treating AIDS, methods of preventing infection by HIV, and methods of treating infection by HIV are also disclosed.

5 DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

This invention is concerned with the compounds of formula I, combinations thereof, or pharmaceutically acceptable salts thereof, in the 10 inhibition of HIV reverse transcriptase, the prevention or treatment of infection by HIV and in the treatment of the resulting acquired immune deficiency syndrome (AIDS). Compounds of the present invention are compounds of Formula I, which includes 15 biotransformed products of an HIV reverse transcriptase inhibitor, L-696,040. Compounds of formula I have the following structure:

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wherein

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R₁ or R₂ or both are substituted at least once with OH;

X is NR, O, S, $\overset{\text{R}}{\underset{\text{CH}}{\text{CH}}}$, $\overset{\text{O}}{\underset{\text{S}}{\text{S}}}$, $\overset{\text{O}}{\underset{\text{SO}_2}{\text{S}}}$, $\overset{\text{OR}}{\underset{\text{C}}{\text{C}}}$, $\overset{\text{OH}}{\underset{\text{CH}}{\text{CH}}}$, $\overset{\text{OH}}{\underset{\text{CH}_2\text{CH}}{\text{CH}_2\text{CH}}}$,

5 $\overset{\text{O}}{\underset{\text{CH}_2\text{C}}{\text{CH}_2\text{C}}}$, $\text{RC}=\text{CR}$, $\overset{\text{O}}{\underset{\text{NCR}}{\text{NCR}}}$, $\text{NCH}_2\text{CO}_2\text{R}$, $\overset{\text{O}}{\underset{\text{NS}}{\text{NS}}}$,

10 $\overset{\text{O}}{\underset{\text{NSO}_2}{\text{NSO}_2}}$, or $\overset{\text{O}}{\underset{\text{NC}}{\text{NC}}}$, where R is H, C₁₋₈ alkyl,

C₁₋₈ alkenyl or C₃₋₈ cycloalkyl;

Z is O, S or NR_X when R_X is H or C₁₋₈ alkyl;

15 n is 0-4;

R₁, R₂ and R₄ are the same or different and are independently

(i) H;

20 (ii) C₁₋₈ alkyl, C₁₋₈ alkenyl,
C₃₋₈cycloalkyl; any of which is
unsubstituted or substituted with one
or two of C₁₋₃ alkoxy, C₁₋₄ alkylamino,
di(C₁₋₄ alkyl)amino, C₁₋₃ alkylthio,
25 hydroxy, amino, oxo, carbonyl,
aminocarbonyl, or oximido, or one to
five of halo;

(iii) C₁₋₅ alkylthio;

(iv) C₁₋₅ alkylsulfinyl;

30 (v) C₁₋₅ alkylsulfonyl;

(vi) C₁₋₅ alkoxy;

(vii) C₁₋₅ alkoxycarbonyl;

(viii) cyano; or

(ix) aryl;

or, R₁ and R₄ may together form a cycloalkyl ring containing 5-7 members;

5 or, R₁ and R₂ may together form a cycloalkyl ring containing 5-7 members;

and R₃ or R₅ are the same or different and are independently

10 (i) H;
(ii) C₁₋₈ alkyl;

(iii) C₁₋₈ alkenyl;
(iv) C₃₋₈ cycloalkyl;
15 —○— is aryl or heterocycle, each unsubstituted or substituted with one or more of

20 (i) C₁₋₆ alkyl unsubstituted or substituted with one or more of A, wherein A is halo, hydroxy, hydroxy-C₁₋₄ alkyl, amino, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino or aryl;
(ii) C₁₋₆ alkenyl unsubstituted or substituted with one or more of A;
25 (iii) C₃₋₆ cycloalkyl unsubstituted or substituted with one or more of A;
(iv) C₁₋₆ alkoxy unsubstituted or substituted with one or more of A;
(v) aryl;
(vi) amino;
30 (vii) C₁₋₆ alkylamino;
(viii) di(C₁₋₆ alkyl)amino;

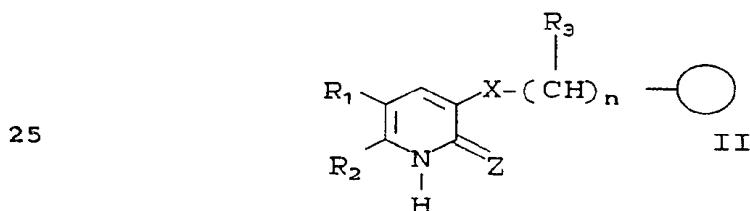
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- 7 -

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- (ix) amino- C_{1-8} alkyl;
- (x) C_{1-8} alkyl-amino- C_{1-8} alkyl;
- (xi) di- $(C_{1-6}$ alkyl)amino C_{1-8} alkyl;
- (xii) C_{1-6} alkoxy carbonyl;
- 5 (xiii) aminocarbonyl;
- (xiv) C_{1-6} alkyl aminocarbonyl;
- (xv) di- $(C_{1-6}$ alkyl)aminocarbonyl;
- (xvi) C_{1-6} alkylthio;
- 10 (xvii) C_{1-6} alkylsulfinyl;
- (xviii) C_{1-6} alkylsulfonyl;
- (xix) hydroxy;
- (xx) halo;
- (xxi) CN; or
- 15 (xxii) NO_2 ;
- with the proviso that heterocycle is not phthalimide;
- or pharmaceutically acceptable salt or ester thereof.

A first embodiment is a compound of formula
20 II,



wherein:
30 X is NH or CH_2 ;
Z is O or S;
n is 1-4;

R_1 is (i) C_{1-8} alkyl, unsubstituted or substituted with one or two of C_{1-3} alkoxy, halo, oxo, hydroxyl, C_{1-4} alkylamino, C_{1-4} -di-alkylamino, or C_{1-3} alkylthio;

5 (ii) C_{1-3} alkylthio;

(iii) C_{1-3} alkoxy; or

R_2 is H, methyl or ethyl, unsubstituted or substituted with one or two of methoxy, 10 hydroxyl, methylamino, dimethylamino or methylthio;

provided that one of R_1 or R_2 , or both, is substituted at least once with hydroxyl;

15 R_3 is H or C_{1-8} alkyl;

$- \bigcirc$ is aryl or heterocycle, each unsubstituted or substituted with one or more of

20 (a) C_{1-6} alkyl,

(b) C_{1-6} alkoxy unsubstituted or substituted with hydroxy- C_{1-4} alkyl,

(c) amino,

(d) C_{1-6} alkyl amino,

(e) di(C_{1-6} alkyl)amino,

25 (f) amino- C_{1-8} alkyl

(g) C_{1-8} alkyl-amino- C_{1-8} alkyl,

(h) di- $(C_{1-6}$ alkyl)amino C_{1-8} alkyl,

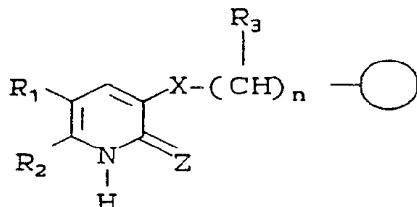
(i) hydroxy, or

(j) halo,

30 with the proviso that heterocycle is not phthalimide, or pharmaceutically acceptable salt or ester thereof.

A second embodiment is further limited to a compound of the formula:

5



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wherein:

X is NH;

Z is O or S;

n is 1-4;

15 R₁ is (i) C₁₋₈ alkyl, unsubstituted or substituted with one or two of C₁₋₃alkoxy, halo, hydroxyl, C₁₋₄alkylamino, C₁₋₄-di-alkylamino, or C₁₋₃ alkylthio;

(ii) C₁₋₃ alkylthio;

20 (iii) C₁₋₃ alkoxy; or

(iv) halo;

R₂ is H, methyl or ethyl, unsubstituted or substituted with one or two of methoxy, hydroxyl, methylamino, dimethylamino or

25 methylthio;

provided that one of R₁ or R₂, or both, is substituted at least once with hydroxyl;

30

R₃ is H or C₁₋₈ alkyl;

—○ is aryl or heterocycle, each unsubstituted or substituted with one or more of

5 (a) C₁₋₆ alkyl,
(b) C₁₋₆ alkoxy unsubstituted or substituted with hydroxy-C₁₋₄ alkyl,
(c) amino,
10 (d) C₁₋₆ alkyl amino,
(e) di(C₁₋₆ alkyl)amino,
(f) amino-C₁₋₈ alkyl,
(g) C₁₋₈ alkyl-amino-C₁₋₈ alkyl,
(h) di-(C₁₋₆ alkyl)amino C₁₋₈ alkyl,
15 (i) hydroxyl, or
(j) halogen,

with the proviso that heterocycle is not phthalimide, or pharmaceutically acceptable salt or ester thereof.

20 A third embodiment is further limited to a compound wherein

R₁ is C₁₋₄ alkyl, unsubstituted or substituted with one or more of hydroxyl;
25 R₂ is H, CH₃ or CH₂OH;
provided that one or R₁ or R₂, or both, is substituted at least once with hydroxyl;

30 aryl is (a) naphthyl, unsubstituted or substituted with one or more of C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen or hydroxyl;

- (b) phenyl, unsubstituted or substituted with one or more of C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen or hydroxyl; or
- (c) biphenyl.

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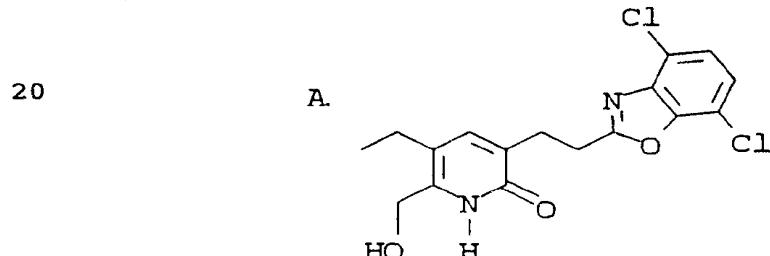
A fourth embodiment is a compound of the first embodiment wherein heterocycle is thienyl, oxazolyl, thiazolyl, triazolyl, pyridyl unsubstituted or substituted with one or more of C₁₋₂ alkoxy or C₁₋₃ alkyl or hydroxy alkyl, pyridinyl, pyrazinyl, benzothienyl, quinolinyl unsubstituted or substituted with C₁₋₂ alkoxy, 5,6,7,8-tetrahydroquino-
10 liny1 unsubstituted or substituted with C₁₋₂ alkoxy, isoquinolinyl unsubstituted or substituted with C₁₋₂ alkoxy, benzimidazolyl, benzofuranyl, benzothiazolyl,
15 benzoxazolyl unsubstituted or substituted with one or more of C₁₋₆ alkyl or halogen or hydroxyl, 4,5,6,7-tetrahydrobenzoxazolyl, naphth [3,2-d] oxazolyl, oxazolo [4,5-b] pyridyl, chromone, or benzo-
20 pyrimidinone.

A fifth embodiment is further limited to a compound wherein heterocycle is 2-oxazolyl, 2-pyridyl, 3-pyridyl unsubstituted or substituted with one or more of C₁₋₂ alkoxy or C₁₋₃ alkyl,
25 2-benzothienyl, 2-quinolinyl, 2-(5,6,7,8-tetrahydroquinolinyl) unsubstituted or substituted with C₁₋₂ alkoxy, 2-benzimidazolyl, 2-benzofuranyl, 2-benzothiazolyl, 2-oxazolo [4,5-b] pyridyl, or 2-benzoxazolyl unsubstituted or
30 substituted with one or more of methyl, halogen or hydroxyl.

A sixth embodiment is further limited to a compound wherein heterocycle is 2-methoxy-5,6-dimethyl-3-pyridyl, 2-methoxy-5-ethyl-6-methyl-3-pyridyl, 3-methoxy-5,6-dimethyl-2-pyridyl, 3-methoxy-5-methyl-6-ethyl-2-pyridyl, 2-benzoxazolyl, 7-methyl-2-benzoxazolyl, 4,7-dimethyl-2-benzoxazolyl, 7-chloro-2-benzoxazolyl, 4,7-dichloro-2-benzo-
xazolyl, 4-fluoro-2-benzoxazolyl, or 4,7-difluoro-2-benzoxazolyl.

10 A seventh embodiment is further limited to a compound wherein Heterocycle is 2-methoxy-5-ethyl-6-methyl-3-pyridyl, 2-benzoxazolyl, 7-methyl-2-benzoxazolyl, 4,7-dimethyl-2-benzoxazolyl, 7-chloro-2-benzoxazolyl, or 4,7-dichloro-2-benzoxazolyl.

15 The most preferred compounds include the following:

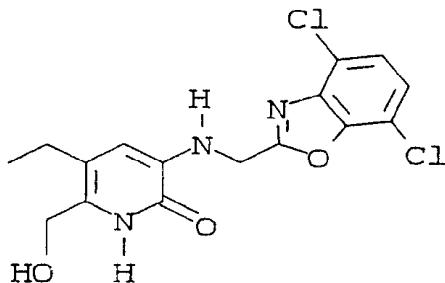


3-[2-(4,7-dichlorobenzoxazol-2-yl)ethyl]-5-ethyl-6-hydroxymethylpyridin-2(1H)-one;

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B.

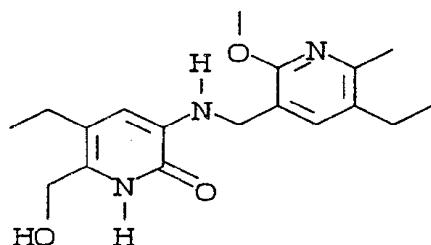


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3-[(4,7-dichlorobenzoxazol-2-yl)methylamino]-5-ethyl-6-hydroxymethylpyridin-2(1H)-one, or

15

C.



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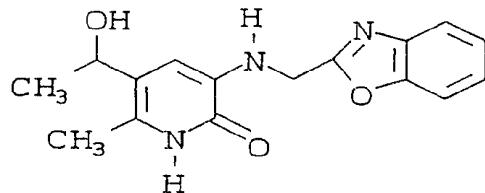
3-{N-[(2-methoxy-5-ethyl-6-methylpyridin-3-yl)methyl]amino}-5-ethyl-6-hydroxymethylpyridin-2(1H)-one,

25 or pharmaceutically acceptable ester thereof.

Other preferred compounds are synthesized by ATCC 53771 from precursor L-696,040, and have the structure:

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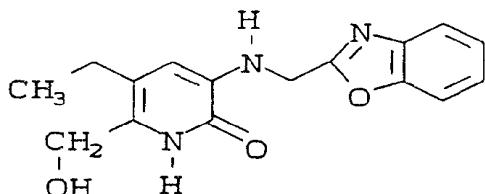


L-697, 913

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or

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L-697, 914

20 or pharmaceutically acceptable ester thereof.

The biotransforming microorganism is
Actinoplanete sp. (Merck Culture Collection MA
 6559), deposited at the American Type Culture
 25 Collection (ATCC 53771).

The compounds of this invention also
 comprise the following:

3-[(benzoxazol-2-yl)methylamino]-5-(1-hydroxyethyl)-6-
 30 methylpyridin-2(1H)-one,
 3-[(benzoxazol-2-yl)methylamino]-5-ethyl-6-hydroxy-
 methylpyridin-2(1H)-one,

155/RDM80

- 15 -

18212IB

3-[2-(benzoxazol-2-yl)ethyl]-5-ethyl-6-hydroxymethyl-
pyridin-2(1H)-one,
3-[(4,7-dimethylbenzoxazol-2-yl)methylamino]-5-ethyl-
6-hydroxymethylpyridin-2(1H)-one,
5 3-[2-(benzoxazol-2-yl)ethyl]-5-(1-hydroxyethyl)-6-
methylpyridin-2(1H)-one,
3-[(4,7-dimethylbenzoxazol-2-yl)methylamino]-5-(1-
hydroxyethyl)-6-methylpyridin-2(1H)-one,
3-[2-(4,7-dichlorobenzoxazol-2-yl)ethyl]-5-ethyl-6-
10 hydroxymethylpyridin-2(H)-one,
3-{N-[(2-methoxy-5-ethyl-6-methylpyridin-3-yl)methyl]-
amino}-5-ethyl-6-hydroxymethylpyridin-2(1H)-one,
3-[(4,7-dichlorobenzoxazol-2-yl)methylamino]-5-ethyl-
6-hydroxymethylpyridin-2(1H)-one,
15 3-[2-(2-methoxy-5-ethyl-6-methylpyridin-3-yl)ethyl]-
5-ethyl-6-hydroxymethylpyridin-2(1H)-one,
3-[(4,7-dichlorobenzoxazol-2-yl)methylamino]-5-(1-
hydroxyethyl)-6-methylpyridin-2(1H)-one,
3-{N-[(2-methoxy-5-ethyl-6-methylpyridin-3-yl)methyl]-
20 amino}-5-(1-hydroxyethyl)-6-methylpyridin-2(1H)-
one,
3-[2-(4,7-Dichlorobenzoxazol-2-yl)ethyl]-5-ethyl-6-
hydroxymethylpyridin-2(1H)-thione,
3-[(4,7-Dichlorobenzoxazol-2-yl)methyl]amino-5-
25 [1(R,S)-hydroxyethyl]-6-methylpyridin-2(1H)-one,
3-[(4,7-Dichlorobenzoxazol-2-yl)methyl]amino-5-(1-
oxoethyl)-6-methylpyridin-2(1H)-one,
3-[(4,7-dichlorobenzoxazol-2-yl)methyl]amino-5-
30 [1(S,R)-hydroxyethyl]-6-methylpyridin-2(1H)-
one,

155/RDM80

- 16 -

18212IB

3-[(5-Ethyl-2-methoxy-6-methylpyridin-3-yl)methyl]-
amino-5-[1(R,S)-hydroxyethyl]-6-methylpyridin-
2(1H)-one,
5-Ethyl-3-[2-(4-fluorobenzoxazol-2-yl)ethyl]-6-
5 hydroxymethylpyridin-2(1H)-one,
3-{N-[(5,6-Dimethyl-3-methoxypyridin-2-yl)methyl]-
amino}-5-ethyl-6-hydroxymethylpyridin-2(1H)-one,
5-Ethyl-6-hydroxymethyl-3-{N-[(3-methoxy-5,6,7,8-
tetrahydroquinolin-2-yl)methyl]amino}pyridin-
10 2(1H)-one,
5-Ethyl-3-{N-[(6-ethyl-3-methoxy-5-methylpyridin-2-
yl)methyl]amino}-6-hydroxymethylpyridin-2(1H)-
one,
3-{N-[(5,6-dimethyl-2-methoxypyridin-3-yl)methyl]-
15 amino}-5-ethyl-6-hydroxymethylpyridin-2(1H)-one,
5-Ethyl-6-hydroxymethyl-3-{N-[(2-methoxy-5,6,7,8-
tetrahydroquinolin-3-yl)methyl]amino}pyridin-2-
(1H)-one,
3-{N-[(2-methoxy-5,6-trimethylene-pyridin-3-yl)-
20 methyl]amino}-5-ethyl-6-hydroxymethylpyridin-2-
(1H)-one,
3-{N-[(6-methoxy-indan-5-yl)methyl]amino}-5-ethyl-
6-hydroxymethylpyridin-2(1H)-one,
3-{N-[(5-ethyl-2-methoxypyridin-3-yl)methyl]amino}-
25 5-ethyl-6-hydroxymethylpyridin-2(1H)-one,
5-Ethyl-6-hydroxymethyl-3-{N-[(2-methoxyquinolin-3-
yl)methyl]amino}pyridin-2(1H)-one,
3-{N-[(3-methoxy-5,6-trimethylene-pyridin-2-yl)-
30 methyl]amino}-5-ethyl-6-hydroxymethylpyridin-
2(1H)-one,
3-{N-[(3-methoxy-5-ethylpyridin-2-yl)methyl]amino}-
5-ethyl-6-hydroxymethylpyridin-2(1H)-one,

3-[N-(5-ethyl-2-methoxybenzyl)amino]-5-ethyl-6-hydroxymethylpyridin-2(1H)-one,

3-[2-(4,7-difluorobenzoxazol-2-yl)ethyl]-5-ethyl-6-hydroxymethylpyridin-2(1H)-one,

5 3-[N-(4,5-dimethyl-2-methoxybenzyl)amino]-5-ethyl-6-hydroxymethylpyridin-2(1H)-one,

or pharmaceutically acceptable salt or ester thereof.

10 The compounds of the present invention, may have asymmetric centers and occur as racemates, racemic mixtures and as individual diastereomers, with all isomeric forms being included in the present invention. Also, combinations of substituents and/or 15 variables are permissible only if such combinations result in stable compounds.

When any variable (e.g., aryl, heterocycle, R₁, R₂, R₃, etc.) occurs more than one time in any constituent or in formula I, its definition on each 20 occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein except where noted, "alkyl" 25 is intended to include both branched- and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge. 30 "Halogen" or "halo" as used herein, means fluoro, chloro, bromo and iodo.

As used herein, with exceptions as noted, "aryl" is intended to mean any stable monocyclic, bicyclic or tricyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic.

5 Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, biphenyl, phenanthryl, anthryl or acenaphthyl.

The term heterocycle or heterocyclic, as used herein except where noted, represents a stable 10 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic or stable 11-15-membered tricyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the 15 group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is 20 fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure.

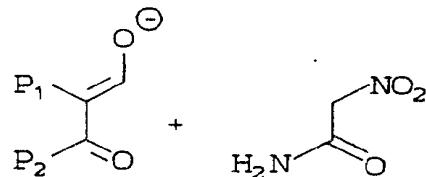
Examples of such heterocyclic elements include 25 thienyl, oxazolyl, thiazolyl, triazolyl, pyridyl, pyrazinyl, benzothienyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzofuranyl, benzothiazolyl, benzoxazolyl unsubstituted or substituted with one or more of C₁₋₆ alkyl or halogen or hydroxyl, naphth [3,2-d] oxazolyl, oxazolo [4,5-b] pyridyl, chromone, 30 or benzopyrimidinone. Heterocycle does not include phthalimide.

The compounds of the present inventions are useful in the inhibition of HIV reverse transcriptase, the prevention or treatment of infection by the human immunodeficiency virus (HIV) and the treatment of 5 consequent pathological conditions such as AIDS. Treating AIDS or preventing or treating infection by HIV is defined as including, but not limited to, treating a wide range of states of HIV infection: AIDS, ARC (AIDS related complex), both symptomatic 10 and asymptomatic, and actual or potential exposure to HIV. For example, the compounds of this invention are useful in treating infection by HIV after suspected past exposure to HIV by e.g., blood transfusion, organ transplant, exchange of body 15 fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

In the organic synthesis of the amino pyridones (3) of this invention, the procedures and protocols of U.S. 3,721,676 can be followed for 20 making many intermediates, which patent is incorporated by reference for these purposes. Applicants here provide preferred methods of synthesis, outlined below.

The 3-nitropyridone of the first step in the 25 synthesis of 3 may be formed by a simultaneous condensation and cyclization of

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155/RDM80

- 20 -

18212IB

in the presence of a base such as piperidinium acetate. Nitroacetamide is prepared according to Brownstein, S.K., J. Org. Chem. 23, 113 (1958).

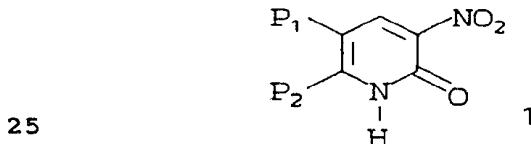
When the side chains R_1 and/or R_2 are 5 hydroxylated, they may have an OH-protecting group (P) such as 2-benzyloxy. P_1 and P_2 are thus defined as:

10 P_1 is R_1- or $P-R_1-$;
 P_2 is R_2- or $P-R_2-$.

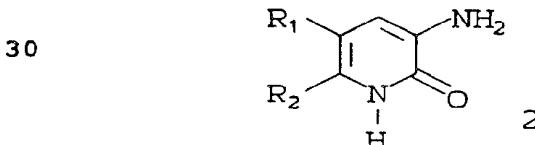
Synthesis of 3 with a hydroxylation on a side chain at the 5-position or 6-position of the amino pyridone ring can be carried out with compounds wherein R_1 or 15 R_2 are protected.

The 3-nitropyridone products of the first step can also be prepared by direct nitration of 3-unsubstituted pyridones. The 3-nitropyridone product of the first step

20



is reduced to

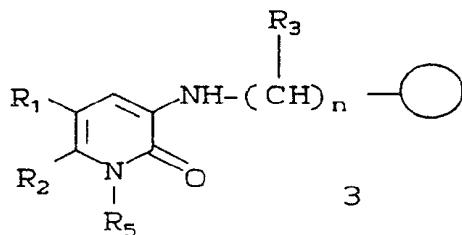


in a second step, preferably by catalytic reduction (when sulfur atoms are not present) in the presence of e.g. H₂ gas and Pd on carbon catalyst in a solvent such as ethanol. See e.g., Okafor, C.O. et al., J.

5 Heterocyclic Chem. 20, 199 (1983). Alternatively the reduction of the second step (including when sulfur atoms are present) can be performed by chemical means, e.g. with NaSH, Na₂S₂O₄, Fe + CaCl₂, H₂S, or Sn + HCl. Reduction with iron in the presence of 10 calcium chlorides is described in Okafor, C.O., J. Org. Chem. 47, 592 (1982). A third step, the final one in the process giving rise to the compounds of this invention,

15

20



involves a coupling reaction, either by alkylation with an alkylhalide or a reductive alkylation with an 25 aldehyde.

Additional reduction by hydrogenation over Pd on carbon can be performed to remove any remaining OH-protecting groups, as needed.

30 Carba derivatives (9), having alkylene bridges between the pyridone ring and the heterocyclic or aromatic entity attached at the 3-position, may be made by the following methods, the first being the preferred method.

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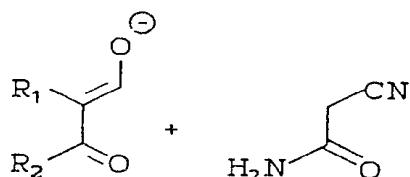
155/RDM80

- 22 -

182121B

In a first step 3-cyano-2-(1H) pyridinone is prepared by a simultaneous condensation and cyclization of

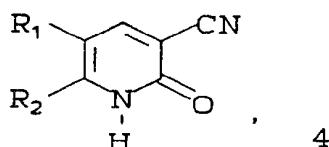
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in the presence of base such as piperidinium acetate or pyrrolidine acetate. The resulting 3-cyano-2-(1H) pyridone,

15

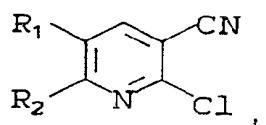


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4

is heated in the presence of phosphorus pentachloride and/or POCl_3 to form the corresponding chloro pyridine,

30

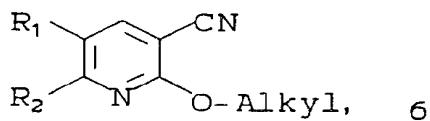


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a conventional method of converting pyridones to chloropyridines. PBr_3 is useful for making the corresponding bromine derivative of product 5.

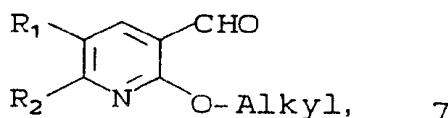
Product 5 is then subjected to nucleophilic
5 substitution to attach an alkoxy protecting group:

10



15 Reduction in the presence of, for example, diisobutyl aluminum hydride, yields

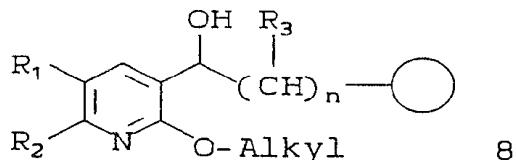
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25 which is a conventional method of reducing nitriles to aldehydes. An alternative reducing agent for the synthesis of 7 is lithium trialkoxy aluminum hydride.

Condensation in the presence of base at very low temperature (preferably at least -100°C) with an
30 alkyl-substituted aryl or alkyl substituted heterocycle yields

5

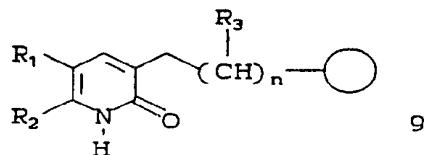


(n = 1)

10

Conditions will vary with the heterocycle to be attached. (The Wittig approach, infra, is preferable when n is more than 1.) Dehydration of the alcohol, and dealkylation followed by hydrogenation results in 15 the compounds of the invention, wherein X = CH₂.

20



(n = 1)

25

The dealkylation is typically carried out with 30 pyridine hydrochloride in the presence of heat. The dehydration need not occur in the same reaction, but may be performed separately by conventional means. The standard catalyst for hydrogenation to produce product 9 is palladium, but other noble metals may

155/RDM80

- 25 -

18212IB

substitute. Alternatively, the hydrogenation can be carried out with diimide or Raney nickel. BCl_3 or BBr_3 at low temperature is useful for performing dealkylation without dehydration. Dealkylation can

5 also be carried out with KI in glacial acetic acid.

A second alternative variation on the final 3 steps is the Wittig approach, wherein the aldehyde derivative (product 7 above) is reacted with aryl or heterocycle, each substituted with alkylene

10 triphenylphosphorane. The resulting condensation yields an unsaturated alkylene bridge, which is then hydrogenated to yield product 9 compounds above. The advantage of the Wittig approach is that it is preferable for synthesis of compounds of formula 9

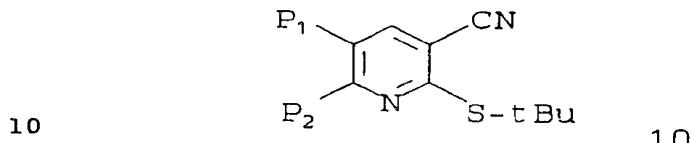
15 wherein n is 2 or more, i.e. with longer alkylene bridges. It is useful when $n=1$. Also, the Wittig approach is preferable for compounds of Formula I having labile substituents on the heterocycle, particularly halogens.

20 A third, more lengthy method of making carba derivatives also exists. Briefly, nitrile (4) is hydrolyzed with acid to the corresponding carboxylic acid. Then a three step conversion to an alcohol is performed, followed by oxidation to aldehyde 7.

25 Condensation of the aryl/heterocycle ring is then carried out with the resulting aldehyde as described above.

2-Thio derivatives (11) are typically prepared by thiolating product 5 above (or its OH-protected analog) with appropriate reagent such as t-butylmercaptan, to yield

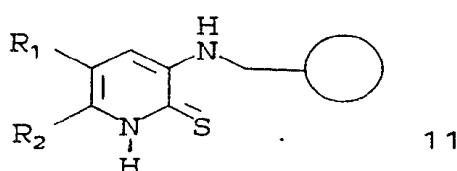
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15 This compound now has a protecting group for the sulfur at the 2-position. The rest of the molecule can be constructed, and, as a final step, dealkylation in pyridine hydrochloride with heat results in the formation of:

20

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Direct thiolation with lawesson's Reagent is also useful for preparing 2-thio derivatives.

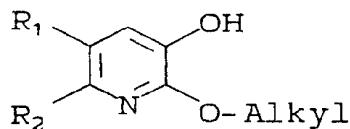
A procedure avails ether linkages at the 3-position of pyridone ring (12). Product 1 above is transformed in three steps into intermediate 12,

155/RDM80

- 27 -

18212IB

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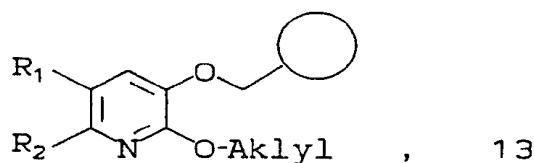


12

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which is subsequently condensed with a halogenated aryl or halogenated heterocycle, in the presence of a base such as sodium hydride to yield

15

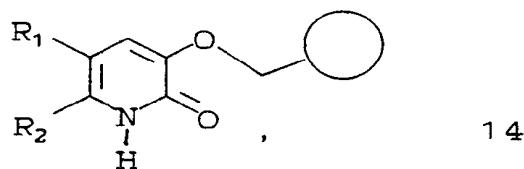


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which is dealkylated with pyridine hydrochloride to yield

25



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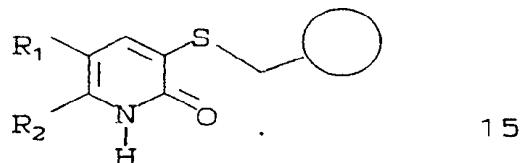
155/RDM80

- 28 -

18212IB

Modification by conventional methodology permits the preparation of the thio analog:

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Dealkylation is conveniently achieved by heating with KI in glacial acetic acid.

15

ATCC DEPOSIT

Before the U.S. filing date of the present application, a sample of the microorganism Actinoplanaceae sp. (Merck Culture Collection MA 6559) was deposited at the American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville MD 20852. The culture access designation is 53771. This deposit will be maintained in the ATCC for at least 30 years and will be made available to the public upon the grant of a patent disclosing it. It should be understood that the availability of a deposit does not constitute a license to practice the subject invention in derogation of patent rights granted by government action.

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155/RDM80

- 29 -

18212IB

GENERAL CHARACTERISTICS OF ATCC 53771

The physical characteristics and taxonomy, including morphological, cultural, biological and physiological characteristics are briefly described hereinbelow.

On the basis of the taxonomic analysis performed thus far, the culture has tentatively been assigned to the order Actionmycetales and to the family Actinoplanacea.

10 This culture grows well on routine media including trypticase soy agar (28° and 37°C), yeast malt extract agar, glycerol asparagine agar, inorganic salt starch agar, oatmeal agar, Czapek Dox, Czapek solution agar and peptone agar, and Bennett's agar, all at 28°C.

15 Morphology - This culture grows as a branched filamentous mycelium with a diameter of 0.2 -0.4 microns. Colonies are opaque, raised, and erose. Colony texture is rubbery on yeast malt extract agar but tends to be butyrous on other media where significant fragmentation of the mycelium is observed. The colony surface tends to be powdery in appearance. No diffusable pigments were observed.

20 Sporangia - are predominantly spherical and range in size from 4 - 25 microns in diameter. Sporangia are generally visible by 21 days and tend to coalesce on glycerol asparagine agar. Spores are rod shaped with blunt ends (0.76 x 1.9 microns), non-motile and occur in long, unbranched chains of up 25 to 150 microns in length.

Cultural characteristics of ATCC 53771Yeast Extract-Malt Extract Agar (ISP Medium 2)

5 Vegetative mycelium is hyaline to yellow,
aerial mycelium develops in 24 - 72 hours and is buff
to rose-pink and powdery in appearance. The reverse
side is tan to reddish brown.

Oatmeal Agar (ISP Medium 3)

10 Vegetative mycelium is hyaline to yellow,
the reverse side is hyaline to tan. Aerial growth is
white to light rose-beige and powdery in appearance.

Inorganic Salts-Starch Agar (ISP Medium 4)

15 Light growth, scant aerial mycelium.
Vegetative growth is hyaline and highly fragmented.
Clearing of starch occurs at periphery of colonies
noted by 7 d.

Glycerol Asparagine Agar (ISP Medium 5)

Vegetative growth is hyaline to yellow, the
reverse side is hyaline to cinnamon brown. Aerial
mycelium is powdery and white to rose-pink.

Peptide-Iron-Yeast Extract Agar (ISP Medium 6)

Vegetative growth is tan. No aerial growth
observed, no melanoid pigments produced.

Tyrosine Agar (ISP Medium 7)

30 Vegetative growth is tan becoming deep
purple as culture ages. Aerial mycelium is velvety
to grayed rose-beige.

Czapek-Dox Agar

Vegetative growth is tan with a pink tone as the culture ages. Aerial mycelia are short and matted with a moist appearance.

5

In general, the compounds L-697,913 and L-697,914 and others can be produced by culturing (fermenting) the ATCC 53771 strain with L-696,040 or other appropriate substrates in an aqueous nutrient 10 medium containing sources of assimilable carbon and nitrogen, preferably under submerged aerobic conditions (e.g. shaking culture, submerged culture, etc.). The aqueous medium is preferably maintained at a pH of about 7 at the initiation and termination 15 (harvest) of the fermentation process. A higher pH leads to substantial and/or total loss of product. The desired pH may be maintained by the use of a buffer such as morpholinoethanesulfonic acid (MES), morpholinopropanesulfonic acid (MOPS), and the like, 20 or by choice of nutrient materials which inherently possess buffering properties, such as production media described hereinbelow.

The preferred sources of carbon in the nutrient medium are carbohydrates such as glucose, 25 xylose, galactose, glycerin, starch, dextrin, and the like. Other sources which may be included are maltose, rhamnose, raffinose, arabinose, mannose, salicin, sodium succinate, and the like.

The preferred sources of nitrogen are yeast 30 extract, meat extract, peptone, gluten meal, cottonseed meal, soybean meal and other vegetable meals (partially or totally defatted), casein

hydrolysates, soybean hydrolysates, and yeast hydrolysates, corn steep liquor, dried yeast, wheat germ, feather meal, peanut powder, distiller's solubles, etc., as well as inorganic and organic 5 nitrogen compounds such as ammonium salts (e.g. ammonium nitrate, ammonium sulfate, ammonium phosphate, etc.), urea, amino acids, and the like.

The carbon and nitrogen sources, though advantageously employed in combination, need not be 10 used in their pure form, because less pure materials which contain traces of growth factors and considerable quantities of mineral nutrients, are also suitable for use. When desired, there may be added to the medium mineral salts such as sodium or 15 calcium carbonate, sodium or potassium phosphate, sodium or potassium chloride, sodium or potassium iodide, magnesium salts, copper salts, cobalt salts, and the like. If necessary, especially when the culture medium foams seriously, a defoaming agent, 20 such as liquid paraffin, fatty oil, plant oil, mineral oil or silicone may be added.

The L-696,040 can be obtained by synthetic organic procedures, as described elsewhere in this application.

25 As to the conditions for the production of L-697,913 or L-697,914 in massive amounts, submerged aerobic cultural conditions are preferred. For the production in small amounts, a shaking or surface culture in a flask or bottle is employed. Further- 30 more, when the growth is carried out in large tanks, it is preferable to use the vegetative form of the organism for inoculation in the production tanks in

order to avoid growth lag in the process of production. Accordingly, it is desirable first to produce a vegetative inoculum of the organism by inoculating a relatively small quantity of culture
5 medium with spores or mycelia of the organism produced in a "slant" and culturing said inoculated medium, also called the "seed medium", and then to transfer the cultured vegetative inoculum aseptically to large tanks. The fermentation medium, in which
10 the inoculum is produced, is generally autoclaved to sterilize the medium prior to inoculation. The pH of the medium is generally adjusted to about 7.0 prior to the autoclaving step by suitable addition of an acid or base, preferably in the form of a buffering
15 solution.

Agitation and aeration of the culture mixture may be accomplished in a variety of ways. Agitation may be provided by a propeller or similar mechanical agitation equipment, by revolving or
20 shaking the fermentor, by various pumping equipment or by the passage of sterile air through the medium. Aeration may be effected by passing sterile air through the fermentation mixture.

The fermentation is usually conducted at a
25 temperature between about 20°C and 40°C, preferably 25-35°C, for a period of about 10 hours to 20 hours, which may be varied according to fermentation conditions and scales. Preferably, the production cultures are incubated for about 17 hours at 27°C on
30 a rotary shaker operating at 220 rpm, wherein the pH of the fermentation medium is maintained at 7.0 to harvest.

Preferred culturing/production media for carrying out the fermentation include the following media:

	Seed Medium A	<u>g/l</u>
5	Dextrose	1.0
	Dextrin	10.0
	Beef Extract	3.0
	Ardamine pH	5.0
	NZ Amine Type E	5.0
10	MgSO ₄ •7H ₂ O	0.05
	K ₂ HPO ₄	0.37
	Adjusted pH to 7.1	
	Add CaCO ₃ 0.5 g/l	

	15 Transformation Medium B	<u>g/l</u>
	Glucose	10
	Hycase SF	2
	Beef Extract	1
	Corn Steep Liquor	3
20	Adjusted pH to 7.0	

	Transformation Medium C	<u>g/l</u>
	Mannitol	5
	Glycerol	5
25	Hycase SF	2
	Beef extract	1
	Corn Steep Liquor	3
	Adjust pH to 7.0	

The produced L-697,913 or L-697,914 can be recovered from the culture medium by conventional means which are commonly used for the recovery of other known biologically active substances. The 5 substances produced are found in the cultured mycelium and filtrate, and accordingly can be isolated and purified from the mycelium and the filtrate, which are obtained by filtering or centrifuging the cultured broth, by a conventional 10 method such as concentration under reduced pressure, lyophilization, extraction with a conventional solvent, such as methylene chloride or methanol and the like, pH adjustment, treatment with a conventional resin (e.g. anion or cation exchange 15 resin, non-ionic adsorption resin, etc.), treatment with a conventional adsorbent (e.g. activated charcoal, silicic acid, silica gel, cellulose, alumina, etc.), crystallization, recrystallization, and the like. A preferred method is solvent 20 extraction, particularly using methylene chloride.

FORMULATIONS

The compounds of the present invention may be administered orally, parenterally (including 25 subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in dosage unit formulations containing conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and 30 vehicles.

Thus, in accordance with the present invention there is further provided a method of treating and a pharmaceutical composition for treating HIV infection and AIDS. The treatment involves

5 administering to a patient in need of such treatment a pharmaceutical composition comprising a pharmaceutical carrier and a therapeutically-effective amount of a compound of the present invention.

10 These pharmaceutical compositions may be in the form of orally-administrable suspensions or tablets; nasal sprays; sterile injectable preparations, for example, as sterile injectable aqueous or oleagenous suspensions or suppositories.

15 When administered orally as a suspension, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate

20 as a suspending agent, methylcellulose as a viscosity enhancer, and sweetners/flavoring agents known in the art. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose

25 and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

When administered by nasal aerosol or inhalation, these compositions are prepared according

30 to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in

saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

5 The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally-acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride
10 solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

When rectally administered in the form of
15 suppositories, these compositions may be prepared by mixing the drug with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquify and/or dissolve in
20 the rectal cavity to release the drug.

The compounds of this invention can be administered orally to humans in a dosage range of 1 to 100 mg/kg body weight in divided doses. One preferred dosage range is 1 to 10 mg/kg body weight
25 orally in divided doses. Another preferred dosage range is 1 to 20 mg/kg body weight orally in divided doses. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon
30 a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body

weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

5 The present invention is also directed to combinations of the HIV reverse transcriptase inhibitor compounds with one or more agents useful in the treatment of AIDS. For example, the compounds of this invention may be effectively administered, 10 whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of the AIDS antivirals, immunomodulators, anti-infectives, such as those in the following Table.

15

TABLEANTIVIRALS

<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
AL-721	Ethigen	ARC, PGL
20	(Los Angeles, CA)	HIV positive, AIDS
Recombinant Human Interferon Beta	Triton Biosciences (Almeda, CA)	AIDS, Kaposi's sarcoma, ARC
25 Acemannan	Carrington Labs (Irving, TX)	ARC (See also immunomodulators)
Cytovene	Syntex	sight threatening CMV
30 Ganciclovir	(Palo Alto, CA)	peripheral CMV retinitis

155/RDM80

- 39 -

18212IB

	<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
	d4T	Bristol-Myers	AIDS, ARC
	Didehydrodeoxy- thymidine	(New York, NY)	
5			
	ddI	Bristol-Myers	AIDS, ARC
	Dideoxyinosine	(New York, NY)	
10	EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection (See also immunomodulators)
15	Trisodium Phosphonoformate	Astra Pharm. Products, Inc. (Westborough, MA)	CMV retinitis, HIV infection, other CMV infections
	Dideoxycytidine; ddC	Hoffman-La Roche (Nutley, NJ)	AIDS, ARC
20	Novapren	Novaferon Labs, Inc. (Akron, OH) Diapren, Inc. (Roseville, MN, marketer)	HIV inhibitor
25	Peptide T Octapeptide Sequence	Peninsula Labs (Belmont, CA)	AIDS
30	Zidovudine; AZT	Burroughs Wellcome (Rsch. Triangle Park, NC)	AIDS, adv, ARC pediatric AIDS, Kaposi's sarcoma, asymptomatic HIV

155/RDM80

- 40 -

18212IB

	<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
5			infection, less severe HIV disease, neurological involve- ment, in combination w/other therapies, post-exposure pro- phylaxis in health care workers
10	Ansamycin LM 427	Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT)	ARC
15	Dextran Sulfate	Ueno Fine Chem. Ind. Ltd. (Osaka, Japan)	AIDS, ARC, HIV positive asymptomatic
20	Virazole Ribavirin	Viratek/ICN (Costa Mesa, CA)	asymptomatic HIV positive, LAS, ARC
25	Alpha Interferon Acyclovir	Burroughs Wellcome (Rsch. Triangle Park, NC) Burroughs Wellcome	Kaposi's sarcoma, HIV in combination w/Retrovir AIDS, ARC, asympto- matic HIV positive, in combination with AZT.

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155/RDM80

- 41 -

18212IB

IMMUNO-MODULATORS

	<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
5	Antibody which neutralizes pH labile alpha aber- rant Interferon	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC
10	in an immuno- adsorption column		
	AS-101	Wyeth-Ayerst Labs. (Philadelphia, PA)	AIDS
15	Bropirimine	Upjohn (Kalamazoo, MI)	advanced AIDS
20	Acemannan	Carrington Labs, Inc. (Irving, TX)	AIDS, ARC (See also anti- virals)
25	CL246,738	American Cyanamid (Pearl River, NY) Lederle Labs (Wayne, NJ)	AIDS, Kaposi's sarcoma
30	EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection (See also anti- virals)
	Gamma Interferon	Genentech (S. San Francisco, CA)	ARC, in combination w/TNF (tumor necrosis factor)

155/RDM80

- 42 -

182121B

	<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
	Granulocyte	Genetics Institute	AIDS
	Macrophage Colony	(Cambridge, MA)	
	Stimulating	Sandoz	
5	Factor	(East Hanover, NJ)	
	Granulocyte	Hoeschst-Roussel	AIDS
	Macrophage Colony	(Somerville, NJ)	
	Stimulating	Immunex	
10	Factor	(Seattle, WA)	
	Granulocyte	Schering-Plough	AIDS
	Macrophage Colony	(Madison, NJ)	
	Stimulating Factor		AIDS, in combination w/AZT
15	HIV Core Particle	Rorer	seropositive HIV
	Immunostimulant	(Ft. Washington, PA)	
20	IL-2	Cetus	AIDS, in combination
	Interleukin-2	(Emeryville, CA)	w/AZT
	IL-2	Hoffman-La Roche	AIDS, ARC, HIV, in
	Interleukin-2	(Nutley, NJ)	combination
25		Immunex	w/AZT
	Immune Globulin	Cutter Biological	pediatric AIDS, in
	Intravenous	(Berkeley, CA)	combination
	(human)		w/AZT
30			

155/RDM80

- 43 -

18212IB

	<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
	IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
5	IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
	Imuthiol Diethyl Dithio Carbamate	Merieux Institute (Miami, FL)	AIDS, ARC
10	Alpha-2 Interferon	Schering Plough (Madison, NJ)	Kaposi's sarcoma w/AZT: AIDS
	Methionine- Enkephalin	TNI Pharmaceutical (Chicago, IL)	AIDS, ARC
15	MTP-PE Muramyl- Tripeptide	Ciba-Geigy Corp. (Summit, NJ)	Kaposi's sarcoma
20	Granulocyte Colony Stimulating Factor	Amgen (Thousand Oaks, CA)	AIDS, in combination w/AZT
25	rCD4 Recombinant Soluble Human CD4	Genentech (S. San Francisco, CA)	AIDS, ARC
30	rCD4-IgG hybrids		AIDS, ARC

155/RDM80

- 44 -

18212IB

	<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
	Recombinant Soluble Human CD4	Biogen (Cambridge, MA)	AIDS, ARC
5	Interferon Alfa 2a	Hoffman-La Roche (Nutley, NJ)	Kaposi's sarcoma AIDS, ARC, in combination w/AZT
10	SK&F106528 Soluble T4	Smith, Kline & French Laboratories (Philadelphia, PA)	HIV infection
15	Thymopentin	Immunobiology Research Institute (Annandale, NJ)	HIV infection
20	Tumor Necrosis Factor; TNF	Genentech (S. San Francisco, CA)	ARC, in combina- tion w/gamma Interferon

ANTI-INFECTIVES

	<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
25	Clindamycin with Primaquine	Upjohn (Kalamazoo, MI)	PCP
30	Fluconazole	Pfizer (New York, NY)	cryptococcal meningitis, candidiasis
	Pastille Nystatin Pastille	Squibb Corp. (Princeton, NJ)	prevention of oral candidiasis

155/RDM80

- 45 -

18212IB

	<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
	Ornidyl	Merrell Dow	PCP
	Eflornithine	(Cincinnati, OH)	
5	Pentamidine	LyphoMed	PCP treatment
	Isethionate (IM & IV)	(Rosemont, IL)	
10	Piritrexim	Burroughs Wellcome (Rsch. Triangle Park, NC)	PCP treatment
	Pentamidine isethionate for inhalation	Fisons Corporation (Bedford, MA)	PCP prophylaxis
15	Spiramycin	Phone-Poulenç Pharmaceuticals (Princeton, NJ)	cryptosporidial diarrhea
20	Intraconazole- R51211	Janssen Pharm. (Piscataway, NJ)	histoplasmosis; cryptococcal meningitis
25	Trimetrexate	Warner-Lambert	PCP

OTHER

	<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
30	Recombinant Human Erythropoietin	Ortho Pharm. Corp. (Raritan, NJ)	severe anemia assoc. and AZT therapy

<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
Megestrol Acetate	Bristol-Myers (New York, NY)	treatment of anorexia assoc. w/AIDS

5

Total Enteral Nutrition	Norwich Eaton Pharmaceuticals (Norwich, NY)	diarrhea and malabsorption related
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10 It will be understood that the scope of combinations of the compounds of this invention with AIDS antivirals, immunomodulators, anti-infectives or vaccines is not limited to the list in the above Table, but includes in principle any combination with
 15 any pharmaceutical composition useful for the treatment of AIDS.

EXAMPLE 1

Preparation of Parent Compound, 3-[(2-Benzoxazolyl-
 20 methyl)amino]-5-ethyl-6-methyl-2-(1H)-pyridinone,
L-696.040

Step A) Preparation of 5-ethyl-6-methyl-3-nitro-2-(1H)-pyridinone

25 A mixture of 2-ethyl-3-oxobutanal, sodium salt (7.5 g, 55 mmol), nitroacetamide (6.6 g, 63 mmol), aqueous piperidinium acetate (4.4 mL) [prepared from glacial acetic acid (42 mL), water

30

(100 mL) and piperidine (72 mL)] in water (45 mL) was stirred at room temperature for 22 hours. The yellow precipitate was collected by filtration and air dried to yield 8.0 g (80%) of 5-ethyl-6-methyl-3-nitro-2-
5 (1H)-pyridinone.

Step B) Preparation of 3-amino-5-ethyl-6-methyl-2-
(1H)-pyridinone

A yellow solution of the 5-ethyl-6-methyl-
10 3-nitro-2-(1H)-pyridinone (10 g, 55 mmol) in a mixture of methanol and tetrahydrofuran (100 mL, 1:1 v/v) was reduced catalytically in the presence of 7% palladium on charcoal (0.7 g) under an atmosphere of hydrogen (50 psi) at room temperature over a period of 3.5
15 hours. The resultant mixture was filtered through a small pad of Celite. The filtrate was concentrated under reduced pressure (15 torr) to provide 5.7 g (68%) of the corresponding aminopyridone.

20 Step C) Preparation of 3-[(2-Benzoxazolymethyl)amino]-
5-ethyl-6-methyl-2-(1H)-pyridinone, L-696,040

A solution of 3-amino-5-ethyl-6-methyl-2-
(1H)-pyridinone (152 mg, 1.0 mmol), 2-chloromethyl-
1,3-benzoxazole (1.07 mmol) and triethylamine (0.14
25 mL, 1.0 mmol) in acetonitrile (10 mL) was stirred at reflux for 24 hours. After concentrating under reduced pressure, the residue was flash chromatographed over silica gel. Elution with 5% MeOH- 95% CHCl₃ gave 132 mg of product which was
30 recrystallized from EtOH-water to give 95 mg of

analytically pure product, mp 202-203°C, with initial melting at 179° followed by resolidification. Anal.

Calcd for $C_{16}H_{17}N_3O_2$:

C, 67.83, H, 6.05; N, 14.83

5 Found: C, 67.71; H, 6.03; N, 14.76.

EXAMPLE 2

Fermentation of L-696,040

A frozen vial (2.0 ml) of culture MA6559

10 (ATCC 53771) was used to inoculate a 250 ml baffled shake flask containing 50 ml of seed medium A. The seed flask was incubated on a rotary shaker (220 rpm) at 27°C for 24 hours. A 1 ml aliquot of the developed seed was used to inoculate a 50 ml 15 non-baffled flask containing 10 ml of transformation medium B; L-696,040 in DMSO was added to the fermentation at 0 hour to achieve a final concentration of 0.05 mg/ml. The shake flask contents were subsequently incubated at 27°C on 20 rotary shaker for two days. The resultant whole both was extracted as described in the next example.

	<u>Media</u>	<u>Seed Medium A</u>	<u>g/l</u>
	Dextrose		1.0
25	Dextrin		10.0
	Beef Extract		3.0
	Ardamine pH		5.0
	NZ Amine Type E		5.0
	$MgSO_4 \cdot 7H_2O$		0.05
30	K_2HPO_4		0.3
	Adjust pH to 7.1		
	Add to $CaCO_3$	0.5 g/l	

<u>Transformation Medium B</u>	<u>g/l</u>
Glucose	10
Hycase SF	2
Beef Extract	1
5 Corn Steep Liquor	3
Adjust pH to 7.0	

EXAMPLE 3Isolation and Purification of Biotransformed Products

10 The whole broth (50 ml) of the preceeding example was adjusted to pH 9 and extracted with methylene chloride (3x50 ml). Methylene chloride extracts were combined and concentrated under vacuum to an oily residue. The residue was dissolved in 15 methanol and subjected to high performance liquid chromatography (HPLC). HPLC was carried out on Whatman Partisil 10 ODS-3, 9.4 mm x 25 cm at room temperature and monitored at 250 nm. The column was developed at 3 ml/min with a linear gradient from 20 0.1% aqueous TFA-CH₃CN, 75:25, to 0.1% aqueous TFA-CH₃CN, 20:80, in 30 minutes. The compounds were collected during repeated injections of the above described extract. The fractions at retention time, 10.5 and 13.5 minutes, were pooled, adjusted to pH 9, 25 respectively, and evaporated to remove acetonitrile. The compounds were then extracted into the methylene chloride to yield 200 µg of L-697,913 and 450 µg of L-697,914, respectively.

155/RDM80

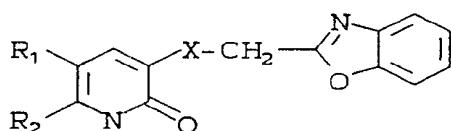
- 50 -

18212IB

EXAMPLE 4
Structure Determination

The structures of two biotransformation
 5 products of L-696,040 (compound 1) were determined by
 NMR. Metabolite 2 was shown to result from
 hydroxylation of the methyl group, while metabolite 3
 from hydroxylation at CH_2 of the ethyl side chain.

10



15

Compd	X	R ₁	R ₂	Sample
1.	NH	CH_2CH_3	CH_3	L-696, 040
2.	NH	CH_2CH_3	CH_2OH	L-697, 914
3.	NH	$\text{CH}(\text{OH})\text{CH}_3$	CH_3	L-697, 913

20

Hydroxylation of the methyl group in 2 was
 25 indicated by the disappearance of methyl singlet near
 2.2 ppm of parent compound 1 and the appearance
 instead of a new singlet at ~4.45 ppm ascribable to
 the CH_2OH protons.

Hydroxylation of C-2 of the ethyl side chain
 30 in 3 was evident from the appearance of the terminal
 methyl group as a doublet (rather than a triplet),
 and the appearance of a CHOH quartet near 4.8 ppm
 instead of the methylene quartet at ~2.25 ppm in the
 parent compound.

155/RDM80

- 51 -

18212IB

EXAMPLE 5Organic Synthesis of L-697,913

5 Steps A-C of Example 1 are repeated, except
that 2-ethyl-3-oxobutanal is substituted with
2-(1-benzyloxy)ethyl-3-oxobutanal. The benzyloxy
protecting group is removed in a final step of
hydrogenation over palladium on carbon, yielding
L-697,913.

10

15

20

EXAMPLE 6Organic Synthesis of L-697,914

25 Steps A-C of Example 1 are repeated, except
that 2-ethyl-3-oxobutanal is substituted with
2-ethyl-3-oxo-4-benzyloxybutanal. The benzyloxy
protecting group is removed in a final step of
hydrogenation over palladium on carbon, yielding
30 L-697,914.

EXAMPLE 7

3-[2-(Benzoxazol-2-yl)ethyl]-5-ethyl-6-hydroxy-methyl-pyridin-2(1H)-one

5 Step 1: Prep of 4-Benzylxy-3-oxo-2-ethylbutanal

A solution of 90% pure 1-(N-morpholino)-1-butene (9.3gm, 60mmol) and triethylamine (8.4mL, 60mmol) in tetrahydrofuran (85mL), under a nitrogen atmosphere, was warmed to 70°C and benzylxyacetyl chloride (9.45mL, 60mmol) was added dropwise via a syringe. The cloudy yellow solution was warmed for 45 minutes and then cooled to room temperature. An aqueous solution of 10% HCl (75mL) was added and the two phase mixture was stirred for 1 hour. This mixture was partitioned into methylene chloride and the organic layer was separated, dried (Na_2SO_4) filtered and the solvent evaporated to give a yellow oil (14.7g) which contained 80% desired product. This oil was used as is.

20

Step 2: Prep. of 3-Cyano-5-ethyl-6-benzylloxymethyl-pyridin-2(1H)-one

To a solution of crude 4-benzylxy-3-oxo-ethylbutanal (6.4gm, 24mmol) and malononitrile (2.22g, 33mmol) in ethanol (30mL) was added acetic acid (2.0mL, 35mmol), followed by dropwise addition of piperidine (2.37 mL, 24mmol) to give a dark reddish brown solution. After stirring for 14 hours a copious precipitate formed. This mixture was warmed at 70°C for 15 hours and then allowed to cool to room temperature. This blackish mixture was diluted with ethanol and the precipitated product was

filtered, rinsed with ethanol and diethyl ether to give off-white product (1.46g), mp: 141-143°C. Additional material was obtained by evaporation of filtrate. Extraction of the residue into chloroform 5 was conducted, and after washing this extract with saturated aqueous NaHCO_3 , filtration through a pad of charcoal was performed. This amber solution was evaporated and the residue triturated with diethyl ether to give additional product (.47g). The 10 estimated yield of this reaction was 30%.

Step 3: Prep. of 2-Benzylxy-3-cyano-5-ethyl-6-benzylxymethylpyridine

To a partial suspension of 3-cyano-5-ethyl-6-15 benzylxymethylpyridin-2(1H)-one (1.36g, 5.08mmol) in dry benzene (20mL) was added benzyl bromide (0.80mL, 6.7mmol) and then silver carbonate (1.43g, 5.2mmol). This mixture was covered with aluminum foil and allowed to stir at room temperature. After 24 hours, 20 the reaction was estimated to be ~80% complete. Additional silver carbonate (.40g, 1.45mmol) was added and the mixture was stirred for another 24 hours until complete. The silver salts were removed by filtration, rinsed with benzene and the combined 25 benzene washings were evaporated to give pure product as an oil (2.09g, quantitative).

Step 4: Prep. of 2-benzylxy-5-ethyl-6-benzylxy-
methyl nictinaldehyde

30 To a solution of 2-benzylxy-3-cyano-5-ethyl-6-benzylxymethylpyridine (2.57g, 6.2mmol) in dry toluene (10mL), under a nitrogen atmosphere in an

156/RDM81

- 54 -

18212IB

ice/acetone bath, was added dropwise a solution of 1.5M diisobutylaluminum hydride/toluene (4.6mL, 6.9mmol). After stirring at room temperature for 15 hours, the reaction was cautiously poured into 10% 5 HCl (30mL), stirred for 0.5 hours and the product extracted into diethyl ether. The ethereal solution was dried, filtered thru a pad of charcoal and evaporated to give a pale yellow oil (1.71g). This oil was further purified by passing a benzene 10 solution through a plug of silica gel to give pure product (1.44g, 55% yield) upon evaporation.

Step 5: Prep of 3-[2-(Benzoxazol-2-yl)ethenyl]-5-
ethyl-6-benzyloxymethyl-2-benzyloxypyridine
15 To a suspension of [(benzoxazol-2-yl)methyl]-
triphenylphosphonium chloride (1.77g, 4.12mmol) in
dry tetrahydrofuran (20mL), under a nitrogen
atmosphere, was added 60% NaH/mineral oil (.42g,
10mmol). After 0.5 hour a solution of 2-benzyloxy-
20 5-ethyl-6-benzyloxymethylnicotinaldehyde (1.44g, 4.0
mmol) in tetrahydrofuran (10mL) was added and the
reaction mixture was refluxed for 23 hours. The
reaction was cooled, neutralized with acetic acid and
partitioned between water and chloroform. The chloro-
25 form layer was washed with NaHCO₃ solution, dried,
filtered through a pad of charcoal and evaporated.
The material was dissolved in chloroform and flash
chromatographed through silica gel to give a pure
product as a yellow oil (1.40g, 74% yield). The
30 product was a mixture of cis and tran olefins (ratio
~0.37).

Step 6: Prep of 3-[2-(Benzoxazol-2-yl)ethyl]-5-ethyl-
6-benzyloxymethylpyridine-2-(1H)-one

A solution of cis/trans 3-[2-(benzoxazol-2-yl)ethenyl]-5-ethyl-6-benzyloxymethyl-2-benzyloxypyridine (1.40g, 2.94mmol) in dry tetrahydrofuran (20mL) and methanol (75mL) containing 10%Pd on charcoal (215mg) as a catalyst was hydrogenated at atmosphere pressure for 20 hours. The catalyst was filtered off and the solution evaporated to give a white residue. This residue was triturated with diethyl ether to give pure product (.78gm, 69% yield), mp: 140-142°C.

Step 7: Prep of 3-[2-(Benzoxazol-2-yl)ethyl]-5-ethyl-
6-hydroxymethylpyridine-2-(1H)-one

A solution of 3-[2-(benzoxazol-2-yl)ethyl]-5-ethyl-6-benzyloxymethylpyridin-2-(1H)-one (198mg, 0.51mmol) in dry methylene chloride (6mL) was cooled in an ice/acetone bath and 1M boron tribromide hexane (1.5mL, 1.5mmol) was added dropwise to give a white precipitate. The suspension was stirred for one hour and then the reaction was quenched by addition of saturated aqueous NaHCO₃ (10mL). After stirring for 0.5 hour, the product was extracted into CH₂Cl₂, dried, filtered and the solvent evaporated to give a solid. Trituration with diethyl ether gave product as a tan solid (138mg, 90% yield). Recrystallization from ethyl acetate afforded a light yellow solid (100mg), mp: 155-156°C.

Anal. Calcd for C₁₇H₁₈N₂O₃: C, 68.44; H, 6.08; N, 9.39
Found: C, 68.15; H, 6.03; N, 9.07

EXAMPLE 8

(\pm)-3-[2-(Benzoxazol-2-yl)ethyl]-5-(1-hydroxyethyl)-6-methylpyridin-2(1H)-one

5 Step A: 2-Benzylxy-5-acetyl-6-methylpyridin-3-carbonitrile

A mixture of 3-cyano-5-acetyl-6-methylpyridin-2(1H)-one (1.76g, 0.01 mol) (L. Mosti et al, J. Het. Chem. 22, 1503 (1985)), benzyl bromide

10 (2.12g, 0.012 mol), silver carbonate (3.06g, 0.011 mol) in benzene was stirred at room temperature under a nitrogen atmosphere overnight, while protected from light. The following day the mixture was filtered, and the solids washed well with benzene. Evaporation of the filtrate gave the desired intermediate (2.47g, 92.8% yield), mp 94-99°C.

Anal. Calcd for $C_{16}H_{14}N_2O_2$ - MW 266.299

C, 72.17; H, 5.30; N 10.52;

Found: C, 71.97; H, 5.30; N, 10.19.

20

Step B: 2-Benzylxy-5-(1-hydroxyethyl)-6-methylpyridin-3-carbonitrile

Sodium borohydride (0.35 g, 0.0092 mol) was added at room temperature to 2-benzylxy-3-cyano-5-acetyl-6-methylpyridin-2(1H)-one (2.44g, 0.0092 mol) in ethanol (60mL). After 2 hours chloroform was added plus a few drops of acetic acid. After washing with water and brine, the chloroform solution was evaporated to give product (2.85g) without further 30 purification.

156/RDM81

- 57 -

18212IB

Step C: 2-Benzyl-5-(1-hydroxyethyl)-6-methylpyridin-3-carboxaldehyde

To a mixture of 2-benzyl-5-(1-hydroxyethyl)-6-methylpyridin-3-carbonitrile (1.00g, 0.0037 mol) in toluene (25 mL), cooled in an ice-acetone bath, was added dropwise diisobutylaluminum hydride (1.5 M in toluene) (5.22 mL, 0.0078 mol). After stirring for one hour under nitrogen the mixture was worked up by quenching into a mixture of excess 1N hydrochloric acid and ice. Extraction with chloroform followed by washing with water, saturated sodium bicarbonate solution, and then brine, and evaporation, gave the desired product (0.091g, 90% yield).

15

Step D: (±)-3-[2-(Benzoxazol-2-yl)ethyl]-5-(1-hydroxyethyl)-6-methyl-2(1H)-pyridinone

The product of step C is then condensed with [(benzoxazol-2-yl)methyl]triphenylphosphonium chloride via the Wittig reaction, then treated with base, in accordance with the procedure and protocols of Example 7, Steps 5-7, yielding the title compounds, mp 185-187°C.

25 ¹H-NMR (DMSO-d₆) 1.08 (d, 3H, J=6.6 Hz), 2.13 (s, 3H), 2.90 (m, 2H), 3.17 (t, 2H, J=6.9 Hz), 4.61 (m, 1H), 4.85 (d, 1H, J=3.9 Hz), 7.4 (m, 2H), 7.5 (m, 2H).
Anal. Calcd. for C₁₇H₁₈N₂O₃ - MW 298.34
C, 68.44; H, 6.08; N, 9.39;
30 Found: C, 68.16; H, 5.85; N, 9.43.

EXAMPLE 9

3-[2-(4,7-Dichlorobenzoxazol-2-yl)ethyl]-5-ethyl-6-hydroxymethylpyridin-2(1H)-one

5 Step A: Preparation of 2-benzyloxy-3[2-(4,7-dichlorobenzoxazol-2-yl)ethenyl]-5-ethyl-6-benzyloxy-methylpyridine

Sodium hydride/mineral oil (60%, 50 mg, 1.2 mmol) was added to a suspension of (4,7-dichlorobenzoxazol-2-yl)methyltriphenylphosphonium chloride (515 mg, 1.03 mmol) in dry tetrahydrofuran (9 mL) under a nitrogen atmosphere. After .75 hours, 2-benzyloxy-5-ethyl-6-benzyloxymethylnicotinaldehyde (375 mg, 1.03 mmol) was added to the yellow suspension and the reaction mixture was refluxed for 1.5 hours. The reaction was cooled, diluted with chloroform, neutralized with a few drops of acetic acid, and washed with water, NaHCO_3 solution, dried (Na_2SO_4) and evaporated. This residue (1.05 g) was dissolved in benzene and flash chromatographed through a plug of silica gel. Appropriate fractions were combined and evaporated to give light oily product (430 mg, 76% yield). NMR indicated that this oil was a 2.3:1 mixture of trans/cis isomers.

25

Step B: Preparation of 3-[2-(4,7-Dichlorobenzoxazol-2-yl)ethyl]-5-ethyl-6-hydroxymethylpyridin-2(1H)-one

A trans/cis mixture of 2-benzyloxy-3-[2-(4,7-dichlorobenzoxazol-2-yl)ethenyl]-5-ethyl-6-benzyloxymethylpyridine (430 mg, 0.78 mmol) was dissolved in methanol (18 mL) and tetrahydrofuran (18 mL) containing 5% palladium/charcoal (154 mg) and

156/RDM81

- 59 -

18212IB

hydrogenated overnight at atmospheric pressure. The catalyst was filtered and the solvent evaporated to give 285 mg of a mixture of products. This material was chromatographed on silica gel eluting with a 5 0.5-5% methanol/chloroform gradient. Appropriate fractions were combined and the solvent evaporated. This residue was triturated with diethyl ether to give 37 mg (13% yield) of product. Recrystallization from ethyl acetate gave 24 mg of analytically pure 10 product, mp 151-152°C;

¹H NMR (300 MHz, CDCl₃) δ 7.33 (1H, s), 7.24 (2H, ABq., J=6.3 Hz), 4.67 (2H, s), 3.35 (2H, t, J=7.3 Hz), 3.14 (2H, t, J=7.3 Hz), 2.36 (2H, ABq., J=7.5 Hz), 1.06 (3H, t, J=7.5 Hz).

Anal. calcd. for C₁₇H₁₆Cl₂N₂O₃:

C, 55.60; H, 4.39; N, 7.63.

Found: C, 55.99; H, 4.40; N, 7.67.

20

EXAMPLE 10

3-[2-(4,7-Dichlorobenzoxazol-2-yl)methylamino]-5-ethyl-6-hydroxymethylpyridin-2(1H)-one

Step A: Preparation of 3-nitro-5-ethyl-6-benzyl oxy-methylpyridin-2(1H)-one

25 Benzyl oxy acetyl chloride (14.2mL, 0.09mol) in dry tetrahydrofuran (10mL) was added dropwise to a solution of 1-(N-morpholino)-1-butene (12.8g, 0.09mol) and triethylamine (12.6mL, 0.09mol) in dry 30 tetrahydrofuran (120mL) warmed at 70°C under a nitrogen atmosphere. After 1.25 hours, the reaction was cooled to room temperature and nitro acetamide

ammonium salt (12.0g, 0.099mol) was added, followed by the dropwise addition of acetic acid (11.4mL, 0.20mol). After stirring for 20-24 hours, the reaction was diluted with chloroform (150mL) and the 5 solution washed with water, 10% HCl, dried (Na₂SO₄) and filtered through a pad of charcoal. The solvent was removed and the residue triturated with cold methanol. The crystalline yellow product was filtered, rinsed with methanol and diethyl ether to 10 give 8.01g (31% yield), mp 157-158°C.

Anal. calcd. for C₁₅H₁₆N₂O₄:

C, 62.49; H, 5.59; N, 9.72.

Found: C, 62.11; H, 5.26; N, 9.68.

15 Step B: Preparation of 3-amino-5-ethyl-6-hydroxy-methylpyridin-2(1H)-one

A solution of 3-nitro-5-ethyl-6-benzyloxy-methylpyridin-2(1H)-one (576mg, 2.0mmol) in tetrahydrofuran (15mL) and methanol (15mL) containing 10% 20 palladium/charcoal (130mg) was hydrogenated at an atmospheric pressure of hydrogen, monitoring the progress by tlc. Additional catalyst was added in 100mg portions after day 2 and day 3. After 3-4 days, the catalyst was filtered and the solvents 25 evaporated. The catalyst was vigorously washed with methanol/chloroform and combined solvents evaporated. The residue was triturated with methylene chloride and product collected by filtration to give 136 mg of 90% pure product. This 30 material was used as is.

Step C: Preparation of 3-[2-(4,7-dichlorobenzoxazol-2-yl)methylamino]-5-ethyl-6-hydroxymethyl-pyridin-2(1H)-one

A suspension of crude 3-amino-5-ethyl-6-hydroxymethylpyridin-2(1H)-one (134mg, 0.80mmol) and 2-iodomethyl-4,7-dichlorobenzoxazole (275mg, 0.83mmol) in acetonitrile (7mL) containing diisopropylethyl-amine (0.96mmol, 125mg) was warmed at 50°C for 4-5 hours. The precipitated product (165 mg) was removed by filtration and chromatographed on silica gel eluting with a 0-3.5% methanol/chloroform gradient. The appropriate fractions were combined, the solvents removed and the residue triturated with diethyl ether to give 95 mg (32% yield) of title compound, mp 193-195°C; ^1H NMR (CDCl_3 , 300MHz) δ 7.38 (2H, s), 6.50 (1H, s), 4.70 (2H, s), 4.49 (2H, s), 2.36 (2H, ABq, J = 7.6Hz) 1.10 (3H, t, J = 7.6 Hz).
Anal. calcd. for $\text{C}_{16}\text{H}_{15}\text{Cl}_2\text{N}_3\text{O}_3$:
C, 52.19; H, 4.11; N, 11.41.
Found: C, 52.11; H, 4.08; N, 11.03.

EXAMPLE 11

3-{N-[(2-Methoxy-5-ethyl-6-methylpyridin-3-yl)methyl]amino}-5-ethyl-6-hydroxymethylpyridin-2(1H)-one

A mixture of crude 3-amino-5-ethyl-6-hydroxymethylpyridin-2(1H)-one (100mg, 0.6mmol) and 2-methoxy-5-ethyl-6-methylnicotinaldehyde (110mg, 0.6mmol) in methanol (3mL) containing 1 drop of acetic acid was stirred at room temperature for 20 hours to give a copious yellow precipitate. Sodium cyanoborohydride (42mg, 0.65mmol) was added to this suspension. The precipitate dissolved and the

156/RDM81

- 62 -

18212IB

product slowly precipitated over 3 hours. The precipitate was filtrated, rinsed with ethanol and diethyl ether and chromatographed on silica gel eluting with 0-3.5% methanol/chloroform gradient.

5 The appropriate fractions were combined, the solvent evaporated and the residue triturated with diethyl ether to give 65mg of title compound, mp 204-205°C; ¹H NMR (CDCl₃, 300MHz) δ 7.26 (1H, s), 6.15 (1H, s), 4.52 (2H, s), 4.23 (2H, s), 3.97 (3H, s), 2.51 (2H, ABq, 10 J = 7.6Hz), 2.42 (3H, s), 2.33 (2H, ABq, J = 7.6Hz), 1.11 (3H, t, J = 7.6Hz), 1.06 (3H, t, J = 7.6Hz) Anal. calcd. for C₁₈H₂₅N₃O₃•0.2H₂O: C, 64.53; H, 7.64; N, 12.54. Found: C, 64.48; H, 7.47; N, 12.37.

15

EXAMPLE 12

3-[2-(2-methoxy-5-ethyl-6-methylpyridin-3-yl)ethyl]-5-ethyl-6-hydroxymethylpyridin-2(1H)-one

20 Step A: Preparation of 2-benzyloxy-3-hydroxymethyl-5-ethyl-6-benzyloxymethylpyridine
To a solution of 2-benzyloxy-5-ethyl-6-benzyloxymethylnicotinaldehyde (1.13 g, 3.13 mmol) in dry tetrahydrofuran (15 mL), under a nitrogen 25 atmosphere was added lithium aluminum hydride (191 mg, 5.0 mmol). The reaction was stirred at room temperature for 2 hours and then warmed to 60°C for one hour. Saturated aqueous sodium sulfate was carefully added to the cooled reaction mixture. 30 Powdered sodium sulfate was then added and the

solution was filtered, the salts rinsed with chloroform and the combined solvents evaporated. The residue was triturated with cold hexane to give crystalline product (893 mg, 78% yield), mp 5 83.5-84.5°C.

Step B: Preparation of 3-[2-(2-methoxy-5-ethyl-6-methylpyridin-3-yl)ethenyl]-5-ethyl-6-benzyl-10 oxyethylpyridin-2(1H)-one

Thionyl chloride (0.37 ml, 5.1 mmol) was added to a solution of 2-benzyloxy-3-hydroxymethyl-5-ethyl-6-benzylloxymethylpyridine (844 mg, 2.32 mmol) in dry benzene (10 mL) and the reaction was warmed at 15 80°C for 2 hours. The solvent and excess thionyl chloride were removed under vacuum and the residue 15 was triturated with diethyl ether to give 341 mg (50% yield) of 3-chloromethyl-5-ethyl-6-benzylloxymethylpyridin-2(1H)-one.

This material was dissolved in tetrahydrofuran (10 mL) and triphenyl phosphine hydrobromide (412 mg, 1.17 mmol) was added. This mixture was refluxed for 3 hours. The copious precipitate was collected by filtration, rinsed with diethyl ether to give 457 mg of a 2:1 mixture of triphenyl[5-ethyl-6-benzylloxymethylpyridin-2(1H)-on-3-yl]phosphonium 25 bromide and 3-chloromethyl-5-ethyl-6-benzylloxymethylpyridin-2(1H)-one as indicated by nmr.

This mixture was suspended in dry tetrahydrofuran (10 mL), under a nitrogen atmosphere, and 80% 30 sodium hydride/mineral oil (89 mg, 3.0 mmol) was added. After stirring at room temperature for 0.5

hour, 2-methoxy-5-ethyl-6-methylnicotinaldehyde (235 mg, 1.3 mmol) was added and the reaction mixture refluxed for 12-20 hours. The cooled reaction was diluted with chloroform (20 mL), acidified with 5 acetic acid and then the separated organic layer was washed with water and saturated aqueous NaHCO_3 . The organic layer was dried (Na_2SO_4), filtered through a charcoal plug and evaporated. This residue was flash chromatographed on silica gel eluting with a 0-1.5% 10 methanol/chloroform gradient to give 638 mg of a 3:2 mixture of cis/trans 3-[2-(2-methoxy-5-ethyl-6-methylpyridin-3-yl)ethenyl]-5-ethyl-6-benzylloxymethylpyridin-2(1H)-one and triphenylphosphine oxide. This mixture was used as is.

15

Step C: Preparation of 3-[2-(2-methoxy-5-ethyl-6-methylpyridin-3-yl)ethyl]-5-ethyl-6-hydroxymethylpyridin-2(1H)-one

The mixture from Step B containing about 20 0.75 mmol of cis/trans 3-[2-(2-methoxy-5-ethyl-6-methylpyridin-3-yl)ethenyl]-5-ethyl-6-benzylloxymethylpyridin-2(1H)-one was dissolved in tetrahydrofuran (15 mL) and methanol (15 mL) containing 5% palladium/charcoal (104 mg) and hydrogenated at atmospheric 25 pressure for 55 hours. The catalyst was filtered and rinsed with chloroform/methanol and the combined organic solutions were evaporated. The residue was triturated with diethyl ether and crystalline by-product triphenyl phosphine oxide was removed by 30 filtration. The resulting filtrate was evaporated to 435 mg of residue which was chromatographed on silica

156/RDM81

- 65 -

18212IB

gel eluting with 0-3% methanol/chloroform gradient. The appropriate fractions were combined, the solvent evaporated and the residue triturated with diethyl ether to give 101 mg (41% yield) of title compound,

5 mp 147-149°C; $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 7.06 (1H, s), 7.04 (1H, s), 4.66 (2H, s), 3.91 (3H, s), 2.78 (4H, br s), 2.48 (2H, ABq, $J=7.6\text{Hz}$), 2.37 (3H, s), 2.34 (2H, ABq, $J=7.6\text{Hz}$), 1.11 (3H, t, $J=7.6\text{Hz}$), 1.05 (3H, t, $J=7.6\text{Hz}$). Anal. Calc'd for $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_3 \cdot 0.35\text{H}_2\text{O}$:

10 C, 67.77; H, 7.89; N, 8.32

Found: C, 67.71; H, 7.92; N, 8.16

EXAMPLE 13

Preparation of 3-[2-(4,7-Difluorobenzoxazol-2-yl)-
15 ethyl]-5-ethyl-6-hydroxymethylpyridin-2(1H)-one

Step A: Preparation of 2-Benzylxy-6-benzylxy-
methy1-3-[2-(4,7-difluorobenzoxazol-2-yl)-
ethenyl]-5-ethylpyridine

20 Sodium hydride (60% in mineral oil, 47 mg, 1.15 mmol) was added to a suspension of [(4,7-difluorobenzoxazol-2-yl)methyl]triphenylphosphonium chloride (512 mg, 1.1 mmol) (prepared by heating 2-chloromethyl-4,7-difluorobenzoxazole with an
25 equimolar amount of triphenylphosphine in refluxing toluene for 15-25 hours) in dry THF (10 mL) under Ar at room temperature. After 15 minutes, 2-benzylxy-6-benzylxy-5-ethylnicotinaldehyde (398 mg, 1.1 mmol) was added and the mixture heated at reflux for
30 15-25 hours. Upon cooling, CHCl_3 was added and after washing with brine the CHCl_3 solution was dried

156/RDM81

- 66 -

18212IB

(Na₂SO₄), filtered and concentrated. The residue was flash chromatographed over silica gel. Pure olefin product was eluted with CHCl₃.

5 Step B: Preparation of 3-[2-(4,7-Difluorobenzoxazol-2-yl)ethyl]-5-ethyl-6-hydroxymethylpyridin-2(1H)-one

A solution of 2-benzyloxy-6-benzyloxymethyl-3-[2-(4,7-difluorobenzoxazol-2-yl)ethenyl]-5-ethyl-10 pyridine (410 mg, 0.82 mmol) in THF (20 mL) MeOH (30 mL) was hydrogenated over a 5% Pd/C catalyst at room temperature and atmospheric pressure for 8 hours until all of the starting material had been consumed. After filtering through diatomaceous earth and 15 concentrating, the residue was flash chromatographed over silica gel. Elution with 3.5% MeOH-96.5% CHCl₃ gave product which was recrystallized from MeOH to 70 mg of analytically pure product, mp=182.5-84°. Anal Calcd for C₁₇H₁₆F₂N₂O₃:

20 C, 61.08; H, 4.82; N, 8.38.
Found: C, 60.88; H, 4.61; N, 8.21.

EXAMPLE 14

Preparation of 5-Cyclpropyl-3-[(4,7-dichlorobenzoxazol-2-yl)methyl]amino]-6-hydroxymethylpyridin-2(1H)-one

Step A: Preparation of 6-Benzylloxymethyl-5-cyclopropyl-3-nitropyridin-2(1H)-one

30 2-Cyclopropylacetaldehyde (42 g, 0.50 mol) is added over 2 hours to a stirred mixture of

morpholine (87 g, 1.0 mol) and K_2CO_3 (69 g, 0.50 mol) cooled to -5° to -10° under Ar. After addition is complete, the cooling bath is removed and the reaction stirred at room temperature overnight.

5 Insoluble salts are removed by filtration and the filtrate distilled to give the enamine.

A solution of this enamine (15.3 g, 100 mmol) and triethylamine (12.6 mL, 90 mmol) in THF (125 mL) is heated to 70° under Ar and treated 10 dropwise over 20 minutes with 2-benzyloxycetyl chloride (14.2 mL, 90 mmol). After stirring at 70° for 1 hour, the mixture is cooled to room temperature and ammonium 2-nitroacetamide (12.1 g, 100 mmol) is added in one portion followed immediately by the 15 dropwise addition of HOAc (11.4 mL) over 10 minutes. The heterogenous mixture is stirred at room temperature overnight. The reaction is diluted with $CHCl_3$ and washed with water and 1N HCl. After drying (Na_2SO_4), filtering and concentrating, the residue is 20 triturated with MeOH and the insoluble solid washed with water and dried to give 6-benzyloxymethyl-5-cyclopropyl-3-nitropyridin-2(1H)-one.

Step B: Preparation of 3-Amino-5-cyclopropyl-6-25 hydroxymethylpyridin-2(1H)-one

A solution of 6-benzyloxymethyl-5-cyclopropyl-3-nitropyridin-2(1H)-one (1.42 g, 50 mmol) in EtOH (50 mL) and THF (50 mL) is hydrogenated over a 5% Pd/C catalyst at room temperature and 32 psi for 30 days. After filtering, solvents are removed under reduced pressure and the residue triturated first with $CHCl_3$ and then with Et_2O to give 3-amino-5-cyclopropyl-6-hydroxymethylpyridin-2(1H)-one.

Step C: Preparation of 5-Cyclopropyl-3-[((4,7-dichlorobenzoxazol-2-yl)methyl)amino]-6-hydroxymethylpyridin-2(1H)-one

A mixture of 3-amino-5-cyclopropyl-6-hydroxy-
5 methylpyridin-2(1H)-one (1.1 g, 6.1 mmol), 2-chloro-
methyl-4,7-dichlorobenzoxazole (1.45 g, 6.1 mmol)
and diisopropylethylamine (1.06 mL, 6.1 mmol) in
acetonitrile (30 mL) is heated at reflux under Ar for
20 hours. After cooling to room temperature,
10 solvents are removed under reduced pressure and the
residue flash chromatographed over silica gel.
Elution with 5% MeOH-95% CHCl₃ gives 5-cyclopropyl-
3-[((4,7-dichlorobenzoxazol-2-yl)methyl)amino]-6-
hydroxymethylpyridin-2(1H)-one.

15

EXAMPLE 15

Preparation of 3-[N-(5-Ethyl-2-methoxybenzyl)amino]-5-ethyl-6-hydroxymethylpyridin-2(1H)-one

Two drops of HOAc are added to a solution of
20 3-amino-5-ethyl-6-hydroxymethylpyridin-2(1H)-one (168
mg, 1.0 mmol) and 5-ethyl-2-methoxybenzaldehyde (162
mg, 1.0 mmol) in MeOH (5 mL) and the solution is
stirred at room temperature for 2 hours. Sodium
borohydride (378 mg, 10 mmol) is added portionwise to
25 the suspension and the reaction stirred at room
temperature for 30 minutes. After diluting with
water and extracting with EtOAc, the organic extract
is washed with brine, dried (Na₂SO₄), filtered and
concentrated. The residue is flash chromatographed
30 over silica gel to give 3-[N-(5-ethyl-2-methoxy-
benzyl)amino]-5-ethyl-6-hydroxymethylpyridin-2(1H)-
one.

EXAMPLE 16Preparation of 3-[N-(4,5-Dimethyl-2-methoxybenzyl)-amino]-5-ethyl-6-hydroxymethylpyridin-2(1H)-one

Two drops of HOAc are added to a solution of
5 3-amino-5-ethyl-6-hydroxymethylpyridin-2(1H)-one (168 mg, 1.0 mmol) and 4,5-dimethyl-2-methoxybenzaldehyde (162 mg, 1.0 mmol) in MeOH (5 mL) and the solution
stirred at room temperature for 2 hours. Sodium
10 borohydride (378 mg, 10 mmol) is added portionwise to
the suspension and the reaction stirred at room
temperature for 30 minutes. After diluting with
water and extracting with EtOAc, the organic extract
is washed with brine, dried (Na_2SO_4), filtered and
concentrated. The residue is flash chromatographed
15 over silica gel to give 3-[N-(4,5-dimethyl-2-methoxy-
benzyl)amino]-5-ethyl-6-hydroxymethylpyridin-2(1H)-
one.

EXAMPLE 17

20 Preparation of 3-[2-(4,7-Dichlorobenzoxazol-2-yl)-ethyl]-5-ethyl-6-hydroxy-methylpyridin-2(1H)-thione

Step A: Preparation of 3-[2-(4,7-dichlorobenzoxazol-2-yl)-ethenyl]-5-ethyl-6-benzyloxymethyl-
25 pyridin-2(1H)-one

A suspension of 2-benzyloxy-3-[2-(4,7-di-chlorobenzoxazol-2-yl)ethynyl]-5-ethyl-6-benzyloxy-methylpyridine (662 mg, 1.21 mmol) [see Example 9, Step A] in glacial acetic acid (25 mL) containing
30 potassium iodide (802 mg, 4.83 mmol) was warmed at 60°C for 2-4 hours. The initial suspension dissolved and the yellow product precipitated. The cooled

suspension was filtered to collect the product which was rinsed with acetic acid, water, methanol and diethyl ether to give 366 mg, mp 233-234°C.

5 Re-filtration of the mother liquors yielded 167 mg of additional product (combined yield 96%). This material was used as is.

Step B: Preparation of 3-[2-(4,7-dichlorobenzoxazol-2-yl)ethyl]-5-ethyl-6-benzyloxymethyl-
10 pyridin-2(1H)-one

A solution of 3-[2-(4,7-dichlorobenzoxazol-2-yl)ethenyl]-5-ethyl-6-benzyloxymethylpyridin-2(1H)-one (250 mg, 0.55 mmol) in tetrahydrofuran (50 mL) containing 10% palladium/carbon (95 mg) was 15 hydrogenated at atmospheric pressure for 15-24 hours. The catalyst was filtered off and the solvent evaporated. The residue was triturated with methanol to give 217 mg (86% yield) of product.

20 Step C: Preparation of 3-[2-(4,7-dichlorobenzoxazol-2-yl)ethyl]-5-ethyl-6-benzyloxymethyl-
pyridin-2(1H)-thione

A suspension of 3-[2-(4,7-dichlorobenzoxazol-2-yl)ethyl]-5-ethyl-6-benzyloxymethylpyridin-2(1H)-one (214 mg, 0.468 mmol) in dry toluene (5 mL) containing 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's Reagent) (231 mg, 0.57 mmol) was warmed at 80°C for four hours to give a clear yellow solution. Upon cooling, methanol (5 mL) was added and the solvents evaporated. The residue was chromatographed on silica gel using a 0-0.5% CH₃CH/CHCl₃ gradient to give 190 mg (85% yield) of product, mp 187-190°C.

Step D: Preparation of 3-[2-(4,7-dichlorobenzoxazol-2-yl)ethyl]-5-ethyl-6-hydroxymethylpyridin-2(1H)-thione

A solution of 3-[2-(4,7-dichlorobenzoxazol-2-yl)ethyl]-5-ethyl-6-benzyloxymethylpyridin-2(1H)-thione (134 mg, 0.28 mmol) in methylene chloride (8 mL) was cooled to -10°C, under an inert atmosphere of nitrogen, and 1M boron trichloride/methylene chloride (0.75 mL, 0.75 mmol) was added dropwise. After 1-2 hours, aqueous NaHCO₃ (5 mL) was added slowly to the cloudy solution. The crude product was extracted into methylene chloride/methanol, dried (Na₂SO₄) and the solvents evaporated. The residue was chromatographed on silica gel and eluted with a 0-1.5% CH₃OH/CHCl₃ gradient. Appropriate fractions were combined, the solvent removed and the residue triturated with CH₂Cl₂/Et₂O to give 34 mg of pure product (31% yield), mp 201-203°C.

¹H NMR (CDCl₃, 300 MHz) δ 7.59 (1H, s), 7.26 (2H, ABq, J=6 Hz), 4.87 (2H, s), 3.45 (4H, m), 2.46 (2H, ABq, J=7 Hz), 1.14 (3H, t, J=7 Hz).

Anal. calc'd for C₁₇H₁₆Cl₂N₂O₂S•0.55 H₂O:

C, 51.92; H, 4.38; N, 7.12.

Found: C, 51.92; H, 4.12; N, 7.01.

25

EXAMPLE 18

Preparation of 3-[[(4,7-Dichlorobenzoxazol-2-yl)-methyl]amino-5-[1(R,S)-hydroxyethyl]-6-methylpyridin-2(1H)-one

Step A: 5-Acetyl-6-methyl-3-nitropyridin-2(1H)-one

A mixture of 3-dimethylaminomethylene-2,4-pentanedione (6.20 g, 0.04 mol) and 2-nitroacetamide (2.08 g, 0.04 mol) in tetrahydrofuran (80 ml) was heated at a bath temperature of 55-60°C under nitrogen for 48 hours. After evaporation to dryness, the residue was extracted with chloroform.

Evaporation of the chloroform, followed by digesting the residue with 2-propanol, gave on filtration the title compound (1.83 g, 20.2% yield), mp 202-207°C.

An analytical sample had mp 207-210°C; ^1H NMR (CDCl_3) δ : 2.5 (s, 3H), 2.87 (s, 3H); 8.95 (s, 1H).

Anal. Calcd. for $\text{C}_8\text{H}_8\text{N}_2\text{O}_2$:

15 C, 48.98; H, 4.11; N, 14.28.

Found: C, 49.19; H, 4.00; N, 14.19.

Step B: 3-Amino-5-(1-hydroxyethyl)-6-methylpyridin-2(1H)-one

20 A combination of 5-acetyl-6-methyl-3-nitropyridin-2(1H)-one (0.80 g, 0.0048 mol), 10% palladium on carbon (0.21 g) in ethanol (200 mL) was stirred under a balloon of hydrogen gas for 2 hours.

Following filtration and evaporation, the residue was 25 dissolved in ethanol (200 mL). A total of 0.55 g of sodium borohydride was added in portions and the reaction mixture stirred for 24 hours. After acidification with acetic acid and evaporation, the crude product was flushed twice with methanol.

30 Chromatography was carried out on a silica gel column employing successively 5%, 10%, and 15%-methanol-methylene chloride mixtures for development. There

was obtained 0.44 g (53% yield) of the title compound, mp >290°C.

¹H NMR (DMSO-d₆) δ: 1.18 (d, J=6.3Hz, 3H); 2.05 (s, 3H); 4.63 (m, 1H); 4.72 (s, 2H); 4.78 (d, J=3.3Hz, 1H); 6.61 (s, 1H); 11.07 (s, 1H).

Anal. Calcd. for C₈H₁₂N₂O₂·0.25 H₂O:

C, 55.64; H, 7.30; N, 16.22.

Found: C, 55.61; H, 7.30; N, 16.18.

10 Step 3: 3-[4,7-Dichlorobenzoxazol-2-yl)methylamino-
5-[1(R,S)-hydroxyethyl]-6-methylpyridin-
2(1H)-one

A mixture of 3-amino-5-(1-hydroxyethyl)-6-methylpyridin-2(1H)-one (0.034 g, 0.0002 mol), 15 4,7-dichloro-2-iodomethylbenzoxazole (0.066 g, 0.0002 mol), diisopropylethylamine (0.028 g, 0.00022 mol) in acetonitrile (5 mL) was heated under nitrogen in a bath maintained at 80°C for 16 hours. The product present after cooling was removed by filtration 20 (0.040 g). Recrystallization was effected by dissolving in 50-50 methanol-methylene chloride (12 mL) with heating. After removing the methylene chloride under vacuum, the desired product crystallized (0.02 g, 27.2% yield), mp 236-238°C 25 (dec).

¹H NMR (DMSO-d₆) δ: 1.14 (d, J=6.3Hz, 3H); 2.06 (s, 3H); 4.61 (m, 1H); 4.67 (m, 2H); 4.76 (d, J=3.6Hz, 1H); 5.94 (t, J=6.3Hz, 1H); 6.53 (s, 1H); 7.50 (d, J=8.7Hz, 1H); 7.54 (d, J=8.7 Hz, 1H); 11.24 (s, 1H).

30

Anal. Calcd. for C₁₆H₁₅Cl₂N₃O₃:

C, 52.19; H, 4.11; N, 11.41.

Found: C, 51.74; H, 4.07; N, 11.10.

EXAMPLE 19Preparation of 3-[(4,7-Dichlorobenzoxazol-2-yl)-methyl]amino-5-acetyl-6-methylpyridin-2(1H)-one

5 A mixture of 3-amino-5-acetyl-6-methylpyridin-2(1H)-one (0.033 g, 0.0002 mol), 4,7-dichloro-2-iodomethylbenzoxazole (0.066 g, 0.0002 mol), and diisopropylethylamine (0.028 g, 0.00022 mol) in acetonitrile (3 mL) was heated at reflux for 24
10 hours. After cooling, the solids obtained on filtration (0.014 g) had mp 300-304°C (dec). A second crop (0.008 g, 35.9% yield overall) was obtained from the filtrate.

15 ¹H NMR (DMSO-d₆) δ: 2.37 (s, 3H); 2.38 (s, 3H); 4.75 (d, J=6.6Hz, 2H); 6.17 (t, J=6.6Hz, 1H); 6.93 (s, 1H); 7.51 (d, J=8.7Hz, 1H); 7.55 (d, J=8.7 Hz, 1H).

Anal. Calcd. for C₁₆H₁₃Cl₂N₃O₃:

16 C, 52.58; H, 3.58; N, 11.47.

20 Found: C, 52.70; H, 3.35; N, 11.36.

EXAMPLE 20Preparation of 3-[(4,7-Dichlorobenzoxazol-2-yl)-methyl]amino-5-[1(R,S)-hydroxyethyl]-6-methylpyridin-2(1H)-one

25 Treatment of the product of Example 19 with sodium borohydride in ethanol results in reduction of the ketone to give the title compound.

EXAMPLE 21

Preparation of 3-[(5-Ethyl-2-methoxy-6-methylpyridin-3-yl)methyl]amino-5-[1(R,S)-hydroxyethyl]-6-methyl-
5 pyridin-2(1H)-one

A mixture of 3-amino-5-(1-hydroxyethyl)-6-methylpyridin-2(1H)-one (0.034 g, 0.0002 mol), 5-ethyl-2-methoxy-6-methylpyridine-3-carboxaldehyde (0.036 g, 0.0002 mol), in toluene (5 mL) containing a 10 drop of acetic acid was heated at reflux for 4 hours. Evaporation afforded a yellow solid (0.065 g) to which was added acetonitrile (3 mL), sodium cyanoborohydride (0.014 g), and acetic acid (0.013 mL). After stirring at room temperature for 6 hours 15 chloroform and water, containing a few drops of acetic acid, were added. The chloroform phase was separated, and washed with saturated sodium bicarbonate, and brine, and then evaporated. The residue was dissolved in methanol with heating. An 20 equal volume of acetonitrile was added and the solution left in the freezer for 20 hours. The product which gradually formed was filtered to give 0.015 g (22.6% yield) of the title compound as a colorless solid, mp 195-196°C.

25 ^1H NMR (CDCl_3) δ : 1.12 (t, $J=7.5\text{Hz}$, 3H); 1.35 (d, $J=6.3\text{Hz}$, 3H); 2.21 (s, 3H); 2.40 (s, 3H); 2.51 (q, $J=7.5\text{Hz}$, 2H); 3.95 (s, 3H); 4.24 (s, 2H); 4.87 (q, $J=6.3\text{Hz}$, 1H); 5.12 (br s, 1H); 6.47 (s, 1H); 7.27 (s, 1H); 10.21 (br s, 1H).

30 Anal. Calcd. for $\text{C}_{18}\text{H}_{25}\text{N}_3\text{O}_3$:

C, 65.24; H, 7.60; N, 12.68.

Found: C, 65.07; H, 7.47; N, 12.99.

EXAMPLE 22Preparation of 5-Ethyl-3-[2-(4-fluorobenzoxazol-2-yl)-ethyl]-6-hydroxymethylpyridin-2(1H)-one

5

Step A: Preparation of 2-Benzylxy-6-benzylxymethyl-5-ethyl-3-[2-(4-fluorobenzoxazol-2-yl)-ethenyl]pyridine

Following the procedure described in Example 10 13, Step A, but substituting 2-chloromethyl-4-fluorobenzoxazole for 2-chloromethyl-4,7-difluorobenzoxazole, the desired title compound of Step A is prepared.

15 Step B: Preparation of 5-Ethyl-3-[2-(4-fluorobenzoxazol-2-yl)ethyl]-6-hydroxymethylpyridin-2(1H)-one

A solution of 2-benzylxy-6-benzylxymethyl-5-ethyl-3-[2-(4-fluorobenzoxazol-2-yl)ethenyl]pyridine (0.66 g, 1.33 mmol) in a mixture of THF (50 mL) and MeOH (75 mL) was hydrogenated over 5% Pd/C (100 mg) at room temp and atmospheric pressure for 18 h. The resultant mixture was filtered and concentrated. The residue was subjected to column chromatography on

25 silica gel eluting with 3.5% MeOH in CHCl_3 .

Collection, concentration, and recrystallization from MeOH yielded 106 mg (25%) of analytically pure product, mp 144-5°C;

30 ^1H NMR (DMSO, 300MHz) δ 7.53 (dd, 1H, J = 7.9, 0.6 Hz), 7.35 (m, 1H), 7.20 (m, 2H), 5.28 (t, 1H, J = 5.5 Hz), 4.28 (d, 2H, J = 5.5 Hz), 3.21 (t, 2H, J = 7.5

156/RDM81

- 77 -

18212IB

Hz), 2.89 (t, 2H, J = 7.5 Hz), 2.28 (q, 2H, J = 7.3 Hz), 0.92 (t, 3H, J = 7.3 Hz).

Anal. Calcd for $C_{17}H_{17}FN_2O_3$:

C, 64.55; H, 5.42; N, 8.86.

5 Found: C, 64.41; H, 5.41; N, 8.70.

EXAMPLE 23

Preparation of 3-{N-[(5,6-Dimethyl-3-methoxypyridin-2-yl)methyl]amino}-5-ethyl-6-hydroxymethylpyridin-2(1H)-one

Step A: Preparation of 2-Methyl-3-oxobutanal, sodium salt

15 To a stirred solution of sodium methoxide (38.6 g, 0.71 mol) in absolute ethanol (90 mL) under an atmosphere of nitrogen, anhydrous diethyl ether (600 mL) was added. The resultant solution was cooled to 0°C, and a mixture of 2-butanone (51.2 g, 0.71 mol) and ethyl formate (57.2 g, 0.77 mol) was added over a period of 3.5 h. The resultant white slurry was stirred at room temperature overnight, filtered, washed with anhydrous diethyl ether (100 mL), and vacuum dried to yield regioselectively 43 g 25 (49.7%) of the desired ketoaldehyde, sodium salt.

Step B: Preparation of 5,6-Dimethyl-3-nitro-2(1H)-pyridinone

30 A mixture of 2-methyl-3-oxobutanal, sodium salt (43 g, 0.35 mol), nitroacetamide (35.6 g, 0.35 mol), aqueous piperidinium acetate (50 mL) [prepared from glacial acetic acid (42 mL), water (300 mL) and

piperidine (72 mL)] in water (45 mL) was stirred at room temperature for 16 hours. The yellow slurry was cooled to 0°C and the precipitate was collected by filtration. The yellow solid obtained was then dried 5 under vacuum overnight to yield 29 g (50%) of 5,6-dimethyl-3-nitro-(1H)-pyridinone.

Step C: Preparation of 2-Chloro-5,6-dimethyl-3-nitropyridine

10 A solution of 3-nitro-5,6-dimethyl-2(1H)-pyridinone (16.8 g, 0.1 mol) in phosphorus oxychloride (100 mL) was heated at 130°C for 6 h. Excess POCl_3 was distilled off under reduced pressure. The residue was poured into vigorously 15 stirred ice-water. The off white solid precipitated was filtered and dissolved in methylene chloride. The resultant solution was washed with saturated aq. sodium bicarbonate, dried over anhydrous sodium sulfate, and passed through a plug of silica gel. 20 Removal of solvent gave 17.2 g (92%) of 2-chloro-5,6-dimethyl-3-nitropyridine.

Step D: Preparation of 3-Amino-5,6-dimethylpyridine

A mixture of 2-chloro-5,6-dimethyl-3-nitropyridine (5 g, 26.8 mmol), triethylamine (10 mL), and 5% Pd/C (0.4 g) in methanol (200 mL) was shaken under an atmosphere of hydrogen (45 - 40 psi) for 16 h. The product mixture was filtered through a plug of Celite and concentrated under reduced 30 pressure. The residue was then triturated with chloroform saturated with ammonia and the resultant slurry filtered through a plug of Celite. The

filtrate was concentrated in vacuum to yield 3.2g (100%) of 3-amino-5,6-dimethylpyridine.

Step E: Preparation of 5,6-Dimethyl-3-hydroxy-pyridine

To a cold (0°C) solution of 3-amino-5,6-dimethylpyridine (4 g, 32.8 mmol) in 5% aq. sulfuric acid (100 mL), a solution of sodium nitrite (2.5 g, 36 mmol) in water (20 mL) was added dropwise. The resultant solution was stirred at 0°C for 30 min, transferred into an addition funnel maintained at 0°C with external cooling, and added dropwise into boiling 5% aq. sulfuric acid (70 mL) over a period of 30 min. The resultant solution was refluxed for additional 15 min, cooled to 0°C, neutralized with 40% aq. sodium hydroxide, saturated with addition of solid sodium chloride, and the product extracted into methylene chloride. The organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to yield 3.5 g (86%) of crude 3-hydroxy-5,6-dimethylpyridine.

Step F: Preparation of 5,6-Dimethyl-2-hydroxymethyl-3-hydroxypyridine

To a solution of 3-hydroxy-5,6-dimethylpyridine (3.5 g, 28.4 mmol) and sodium hydroxide (1.2 g, 28.4 mmol) in water (12 mL) at 90°C, 38% aq. formaldehyde was added in four 2.5 mL aliquots in 90 min intervals. The resultant solution was heated at 90°C for additional 90 min, neutralized with acetic

acid, and concentrated under reduced pressure. The residue was triturated with 10% methanol in chloroform saturated with ammonia, and filtered through a plug of Celite. The filtrate was 5 concentrated and the residue subjected to column chromatography on silica gel eluted with 10% methanol in chloroform. Collection and concentration of appropriate fractions gave 2.1 g (48%) of 2-hydroxymethyl-3-hydroxy-5,6-dimethylpyridine.

10

Step G: Preparation of 5,6-Dimethyl-2-hydroxymethyl-3-methoxypyridine

To a solution of 2-hydroxymethyl-3-hydroxy-5,6-dimethylpyridine (1.16 g, 7.6 mmol) and sodium 15 hydride (0.18 g, 7.6 mmol) in anhydrous dimethyl-formamide (20 mL) at 0°C, methyl iodide (1.08 g, 7.6 mmol) was added and stirred at 0°C for 30 min, and at room temp for 1 h. The resultant solution was concentrated under reduced pressure, and the residue 20 subjected to column chromatography on silica gel eluted with 2% methanol in chloroform. Collection and concentration of appropriate fractions gave 0.7 g (55%) of 2-hydroxymethyl-3-methoxy-5,6-dimethylpyridine.

25

Step H: Preparation of 5,6-Dimethyl-3-methoxy-2-picinaldehyde

A slurry of 2-hydroxymethyl-3-methoxy-5,6-dimethylpyridine (0.7 g, 4.2 mmol) and activated 30 manganese (IV) oxide (8 g) in methylene chloride (40 mL) was stirred at rt overnight. The resultant

156/RDM81

- 81 -

18212IB

mixture was filtered through a plug of Celite and the filtrate concentrated to give 0.4 g (58%) of 5,6-dimethyl-3-methoxy-2-picinaldehyde.

5 Step I: Preparation of 3-[N-[(5,6-Dimethyl-3-methoxypyridin-2-yl)methyl]amino]-5-ethyl-6-hydroxymethylpyridin-2(1H)-one
A solution of 3-amino-5-ethyl-6-hydroxymethylpyridin-2(1H)-one (100 mg, 0.59 mmol),
10 5,6-dimethyl-3-methoxy-2-picinaldehyde (98 mg, 0.59 mmol), and acetic acid (20 μ L) in methanol (5 mL) was stirred at room temp for 17 h. The resultant yellow solution was treated with sodium borohydride until the solution became colorless. The product solution
15 was then concentrated onto silica gel (2 g), and subjected to column chromatography on silica gel eluting with 3.5-5% methanol in chloroform gradient. Collection, concentration of appropriate fraction, and recrystallization from a mixture of
20 acetonitrile-methanol-water yielded 38 mg (20%) of the title compound, mp 202-5°C;
 1 H NMR (DMSO, 300MHz) δ 7.25 (s, 1H), 6.23 (s, 1H), 5.99 (t, 1H, J = 5 Hz), 4.90 (t, 1H, J = 5 Hz), 4.22 (d, 2H, J = 5 Hz), 4.15 (d, 2H, J = 5 Hz), 3.82 (s, 25 3H), 2.37 (m, 5H), 2.25 (s, 3H), 1.07 (t, 3H, J = 7.3 Hz).

Anal. Calcd for $C_{17}H_{23}N_3O_3$:

C, 64.33; H, 7.30; N, 13.24.

Found: C, 64.22; H, 6.93; N, 13.17.

EXAMPLE 24

Preparation of 5-Ethyl-6-hydroxymethyl-3-{N-[(3-methoxy-5,6,7,8-tetrahydroquinolin-2-yl)methyl]-
5 aminopyridin-2(1H)-one

Following procedures described in Example 23
and starting with cyclohexanone, 5-Ethyl-6-hydroxymethyl-3-{N-[(3-methoxy-5,6,7,8-tetrahydroquinolin-2-yl)methylamino}pyridin-2(1H)-one, mp

10 194-5°C (acetonitrile) was prepared.

¹H NMR (CDCl₃, 300MHz) δ 7.26 (s, 1H), 6.42 (s, 1H),
4.64 (br s, 2H), 4.56 (br s, 2H), 3.97 (s, 3H), 3.05
(t, 2H, J = 5 Hz), 2.83 (t, 2H, J = 5 Hz), 2.39 (q,
2H, J = 7.3 Hz), 1.82 (m, 4H), 1.07 (t, 3H, J = 7.3

15 Hz).

Anal. Calcd for C₁₉H₂₅N₃O₃ · 0.3 H₂O:
C, 65.42; H, 7.40; N, 12.05.

Found: C, 65.44; H, 7.11; N, 12.02.

20

Example 25

Preparation of 5-Ethyl-3-{N-[(6-ethyl-3-methoxy-5-methylpyridin-2-yl)methylamino]-6-hydroxymethylpyridin-2(1H)-one

25 Following procedures described in Example 23
and starting with 2-pentanone, 5-Ethyl-3-{N-[(6-ethyl-3-methoxy-5-methylpyridin-2-yl)methylamino]-6-hydroxymethylpyridin-2(1H)-one, mp 193-5°C
(acetonitrile) was prepared.

30 ¹H NMR (CDCl₃; 300MHz) δ 7.08 (s, 1H), 6.46 (s, 1H),
4.56 (br s, 2H), 4.46 (br s, 2H), 3.90 (s, 3H), 2.85
(q, 2H, J = 7.5 Hz), 2.40 (q, 2H, J = 7.5 Hz), 2.34

156/RDM81

- 83 -

18212IB

(s, 3H), 1.29 (t, 3H, J = 7.5 Hz), 1.12 (t, 3H, J = 7.5 Hz).

Anal. Calcd for $C_{18}H_{25}N_3O_3$. 0.25 H_2O :
C, 64.36; H, 7.65; N, 12.51.

5 Found: C, 64.57; H, 7.35; N, 12.12.

EXAMPLE 26

10 Preparation of 3-{N-[(5,6-Dimethyl-2-methoxypyridin-3-yl)methyl]amino}-5-ethyl-6-hydroxymethylpyridin-2(1H)-one

15 Following the procedures described in Example 11 and starting with 5,6-dimethyl-2-methoxynicotinaldehyde, the title compound is obtained.

EXAMPLE 27

20 Preparation of 5-Ethyl-6-hydroxymethyl-3-{N-[(2-methoxy-5,6,7,8-tetrahydroquinolin-3-yl)methyl]amino}pyridin-2(1H)-one

Following the procedures described in Example 11 and starting with 2-methoxy-5,6,7,8-tetrahydroquinoline-3-carboxaldehyde, the title compound is obtained.

EXAMPLE 28

25 Preparation of 3-{N-[(2-Methoxy-5,6-trimethylene-pyridin-3-yl)methyl]amino}-5-ethyl-6-hydroxymethylpyridin-2(1H)-one

30 Following the procedures described in Example 11 and starting with 2-methoxy-5,6-trimethylene-nicotinaldehyde, the title compound is obtained.

EXAMPLE 29

Preparation of 3-{N-[(5-Ethyl-2-methoxypyridin-3-yl)-methyllamino]-5-ethyl-6-hydroxymethylpyridin-2(1H)-one}

Following the procedures of Example 11 and
5 starting with 5-ethyl-2-methoxynicotinaldehyde, the
title compound is obtained.

EXAMPLE 30

10 Preparation of 5-Ethyl-6-hydroxymethyl-3-{N-[(2-methoxyquinolin-3-yl)methyl]amino}pyridin-2(1H)-one

Following the procedures of Example 11 and
starting with 2-methoxyquinoline-3-carboxaldehyde,
15 the title compound is obtained.

EXAMPLE 31

20 Preparation of 3-{N-[(3-Methoxy-5,6-trimethylene-pyridin-2-yl)methyl]amino}-5-ethyl-6-hydroxymethylpyridin-2(1H)-one

Following the procedures of Example 11 and
starting with 3-methoxy-5,6-trimethylene-2-picinaldehyde,
25 the title compound is obtained.

EXAMPLE 32

30 Preparation of 3-{N-[(3-Methoxy-6-ethylpyridin-2-yl)-methyl]amino}-5-ethyl-6-hydroxymethylpyridin-2(1H)-one

Following the procedures of Example 11 and
starting with 3-methoxy-6-ethyl-2-picinaldehyde,
the title compound is obtained.

EXAMPLE 33

Preparation of 5-Ethyl-6-hydroxymethyl-3-{N-[(3-methoxyquinolin-2-yl)methyl]amino}pyridin-2(1H)-one

Following the procedures of Example 11 and starting with 3-methoxyquinoline-2-carboxaldehyde, the title compound is obtained.

10

EXAMPLEReverse Transcriptase Assay

The assay measures the incorporation of tritiated deoxyguanosine monophosphate by recombinant HIV reverse transcriptase (HIV RT_R) (or other RT) into acid-precipitable cDNA at the Km values of dGTP and poly r(C)•oligo d(G)₁₂₋₁₈. The inhibitors of the present invention inhibit this incorporation.

Thirty μ L of a reaction mixture containing equal volumes of: 500 mM Tris•HCl (pH 8.2), 300 mM MgCl₂, 1200 mM KCl, 10 mM DTT, 400 μ g/mL poly r(C)•oligo d(G) [prepared by dissolving 1.5 mg (25 U) poly r(C)•oligo d(G) in 1.5 ml sterile distilled H₂O and diluting to 400 μ g/ml], 0.1 μ Ci/ μ l [³H] dGTP, 160 μ M dGTP, was added to 10 μ l sterile distilled H₂O, 2.5 μ l of potential inhibitor and 10 μ L of 5 nM purified HIV RT_R in tubes. The mixture was incubated at 37°C for 45 minutes.

After incubation is complete, the tubes were cooled in ice for 5 minutes. Ice-cold 13% TCA containing 10 mM NaPP_i (200 μ l) are added and the mixture incubated on ice for 30 minutes. The

precipitated cDNA is removed by filtration using presoaked glass filters [TCA, NaPP_i]. The precipitate is then washed with 1N HCl, 10 mM NaPP_i.

5 The filter discs are then counted in a scintillation counter.

Under these conditions [dGTP] and poly r(C)ⁿoligo d(G)₁₂₋₁₈ each are approximately equal to the appropriate Km value. Approximately 5-6,000 cpm of [³H] GMP are incorporated into acid-precipitable 10 material. The RT reaction is concentration- and time-dependent. DMSO (up to 5%) does not affect enzyme activity. Calculated IC₅₀ values for the lead compounds of this invention were approximately 94nM and (more than or equal to) 300 μ M for L-697,914 and 15 L-697,913, respectively. Other preferred compounds gave IC₅₀ values of between about 5nM and about 100nM, the most preferred having IC₅₀ values between about 11nM and 14nM.

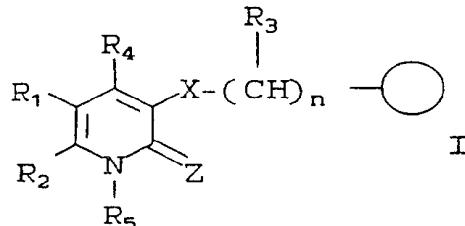
20 While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations, and modifications, as come within the scope of the 25 following claims and its equivalents.

WHAT IS CLAIMED IS:

1. A compound of the formula

5

10



wherein

15

R_1 or R_2 or both are substituted at least once with OH;

X is NR , O , S , $\overset{R}{\underset{|}{\text{CH}}}$, $\overset{O}{\underset{||}{\text{S}}}$, $\overset{O}{\underset{||}{\text{SO}_2}}$, $\overset{OR}{\underset{||}{\text{C}}}$, $\overset{OH}{\underset{|}{\text{CH}}}$, $\overset{OH}{\underset{|}{\text{CH}_2\text{CH}}}$,

20

$\overset{O}{\underset{||}{\text{CH}_2\text{C}}}$, RC=CR , $\overset{O}{\underset{||}{\text{NCR}}}$, $\overset{O}{\underset{||}{\text{NCH}_2\text{CO}_2\text{R}}}$, $\overset{O}{\underset{||}{\text{NS}}}$,

25

$\overset{O}{\underset{||}{\text{NSO}_2}}$, or $\overset{O}{\underset{||}{\text{NC}}}$, where R is H, C_{1-8} alkyl,

30

C_{1-8} alkenyl or C_{3-8} cycloalkyl;

Z is O, S or NR_x when R_x is H or C_{1-8} alkyl;

n is 0-4;

R_1 , R_2 and R_4 are the same or different and are independently

(i) H;
(ii) C₁₋₈ alkyl, C₁₋₈ alkenyl,
C₃₋₈cycloalkyl; any of which is
unsubstituted or substituted with one
5 or two of C₁₋₃ alkoxy, C₁₋₄ alkylamino,
di(C₁₋₄ alkyl)amino, C₁₋₃ alkylthio,
hydroxy, amino, oxo, carbonyl,
aminocarbonyl, or oximido, or one to
five of halo;
10 (iii) C₁₋₅ alkylthio;
(iv) C₁₋₅ alkylsulfinyl;
(v) C₁₋₅ alkylsulfonyl;
(vi) C₁₋₅ alkoxy;
15 (vii) C₁₋₅ alkoxy carbonyl;
(viii) cyano; or
(ix) aryl;
or, R₁ and R₄ may together form a cycloalkyl ring
containing 5-7 members;

20 or, R₁ and R₂ may together form a cycloalkyl ring
containing 5-7 members;

and R₃ or R₅ are the same or different and are
independently

25 (i) H;
(ii) C₁₋₈ alkyl;
(iii) C₁₋₈ alkenyl;
(iv) C₃₋₈ cycloalkyl;
30 —○— is aryl or heterocycle, each unsubstituted or
substituted with one or more of

(i) C_{1-6} alkyl unsubstituted or substituted with one or more of A, wherein A is halo, hydroxy, hydroxy- C_{1-4} alkyl, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino or aryl;

5 (ii) C_{1-6} alkenyl unsubstituted or substituted with one or more of A;

(iii) C_{3-6} cycloalkyl unsubstituted or substituted with one or more of A;

10 (iv) C_{1-6} alkoxy unsubstituted or substituted with one or more of A;

(v) aryl;

(vi) amino;

15 (vii) C_{1-6} alkylamino;

(viii) di(C_{1-6} alkyl)amino;

(ix) amino- C_{1-8} alkyl;

(x) C_{1-8} alkyl-amino- C_{1-8} alkyl;

(xi) di- $(C_{1-6}$ alkyl)amino C_{1-8} alkyl;

20 (xii) C_{1-6} alkoxy carbonyl;

(xiii) aminocarbonyl;

(xiv) C_{1-6} alkyl aminocarbonyl;

(xv) di(C_{1-6} alkyl)aminocarbonyl;

(xvi) C_{1-6} alkylthio;

25 (xvii) C_{1-6} alkylsulfinyl;

(xviii) C_{1-6} alkylsulfonyl;

(xix) hydroxy;

(xx) halo;

(xxi) CN; or

(xxii) NO_2 ;

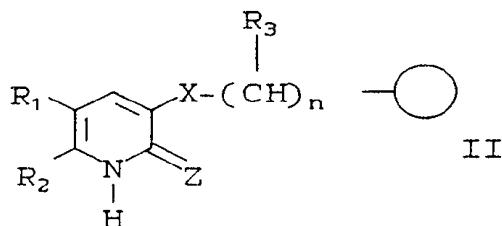
30 with the proviso that heterocycle is not phthalimide;

or pharmaceutically acceptable salt or ester thereof.

2. A compound according to Claim 1 of the formula

5

10



wherein:

15 X is NH or CH2;

Z is O or S;

n is 1-4;

20 R1 is (i) C1-8 alkyl, unsubstituted or substituted with one or two of C1-3alkoxy, halo, oxo, hydroxyl, C1-4alkylamino, C1-4-di-alkylamino, or C1-3 alkylthio;

(ii) C1-3 alkylthio;

(iii) C1-3 alkoxy; or

25 R2 is H, methyl or ethyl, unsubstituted or substituted with one or two of methoxy, hydroxyl, methylamino, dimethylamino or methylthio;

provided that one of R1 or R2, or both, is substituted at least once with hydroxyl;

30 R3 is H or C1-8 alkyl;

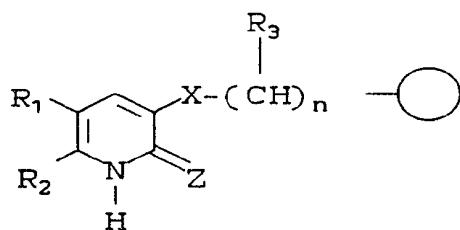
—○ is aryl or heterocycle, each unsubstituted or substituted with one or more of

- (a) C₁₋₆ alkyl,
- (b) C₁₋₆ alkoxy unsubstituted or substituted with hydroxy-C₁₋₄ alkyl,
- (c) amino,
- (d) C₁₋₆ alkyl amino,
- (e) di(C₁₋₆ alkyl)amino,
- (f) amino- C₁₋₈ alkyl
- (g) C₁₋₈ alkyl-amino-C₁₋₈ alkyl,
- (h) di-(C₁₋₆ alkyl)amino C₁₋₈ alkyl,
- (i) hydroxy, or
- (j) halo,

15

with the proviso that heterocycle is not phthalimide, or pharmaceutically acceptable salt or ester thereof.

3. A compound according to Claim 2, of the
20 formula



20 wherein:

30 x is NH.

Z is 0 or 5.

— 15 —

R₁ is (i) C₁₋₈ alkyl, unsubstituted or substituted with one or two of C₁₋₃alkoxy, halo, hydroxyl, C₁₋₄alkylamino, C₁₋₄-di-alkylamino, or C₁₋₃ alkylthio;

5 (ii) C₁₋₃ alkylthio;
(iii) C₁₋₃ alkoxy; or
(iv) halo;

R₂ is H, methyl or ethyl, unsubstituted or substituted with one or two of methoxy, 10 hydroxyl, methylamino, dimethylamino or methylthio;

provided that one of R₁ or R₂, or both, is substituted at least once with hydroxyl;

15 R₃ is H or C₁₋₈ alkyl;

—○— is aryl or heterocycle, each unsubstituted or substituted with one or more of
(a) C₁₋₆ alkyl,
(b) C₁₋₆ alkoxy unsubstituted or 20 substituted with hydroxy-C₁₋₄ alkyl,
(c) amino,
(d) C₁₋₆ alkyl amino,
(e) di(C₁₋₆ alkyl)amino,
(f) amino- C₁₋₈ alkyl,
25 (g) C₁₋₈ alkyl-amino-C₁₋₈ alkyl,
(h) di-(C₁₋₆ alkyl)amino C₁₋₈ alkyl,
(i) hydroxyl, or
(j) halogen,

30 with the proviso that heterocycle is not phthalimide, or pharmaceutically acceptable salt or ester thereof.

4. A compound of claim 3, wherein:

R₁ is C₁₋₄ alkyl, unsubstituted or substituted with one or more of hydroxyl;

5

R₂ is H, CH₃ or CH₂OH;
provided that one of R₁ or R₂, or both, is substituted at least once with hydroxyl;

10 aryl is (a) naphthyl, unsubstituted or substituted with one or more of C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen or hydroxyl;
(b) phenyl, unsubstituted or substituted with one or more of C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen or hydroxyl; or
15 (c) biphenyl.

5. A compound of Claim 2 wherein heterocycle is thienyl, oxazolyl, thiazolyl, 20 triazolyl, pyridyl unsubstituted or substituted with one or more of C₁₋₂alkoxy or C₁₋₃alkyl or hydroxy-alkyl, pyridinonyl, pyrazinyl, benzothienyl, quinolinyl unsubstituted or substituted with C₁₋₂ alkoxy, 5,6,7,8-tetrahydroquinolinyl unsubstituted or 25 substituted with C₁₋₂ alkoxy, isoquinolinyl unsubstituted or substituted with C₁₋₂ alkoxy, benzimidazolyl, benzofuranyl, benzothiazolyl, benzoxazolyl unsubstituted or substituted with one or more of C₁₋₆ alkyl or halogen or hydroxyl, 30 4,5,6,7-tetrahydrobenzoxazolyl, naphth [3,2-d] oxazolyl, oxazolo [4,5-b] pyridyl, chromone, or benzopyrimidinone.

6. A compound of Claim 5 wherein
heterocycle is 2-oxazolyl, 2-pyridyl, 3-pyridyl
unsubstituted or substituted with one or more of
C₁₋₂alkoxy or C₁₋₃alkyl, 2-benzothienyl,
5 2-quinolinyl, 2-(5,6,7,8-tetrahydroquinolinyl)
unsubstituted or substituted with C₁₋₂ alkoxy,
2-benzimidazolyl, 2-benzofuranyl, 2-benzothiazolyl,
2-oxazolo [4,5-b] pyridyl, or 2-benzoxazolyl
10 unsubstituted or substituted with one or more of
methyl, halogen or hydroxyl.

7. A compound of Claim 6 wherein
heterocycle is 2-methoxy-5,6-dimethyl-3-pyridyl,
2-methoxy-5-ethyl-6-methyl-3-pyridyl,
15 3-methoxy-5,6-dimethyl-2-pyridyl, 3-methoxy-5-
methyl-6-ethyl-2-pyridyl, 2-benzoxazolyl,
7-methyl-2-benzoxazolyl, 4,7-dimethyl-2-benzoxazolyl,
7-chloro-2-benzoxazolyl, 4,7-dichloro-2-
20 benzoxazolyl, 4-fluoro-2-benzoxazolyl, or 4,7-di-
fluoro-2-benzoxazolyl.

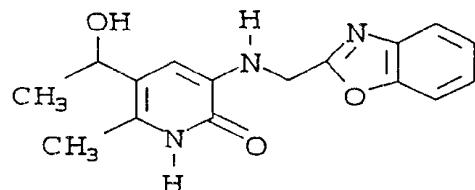
8. A compound of claim 7 wherein
Heterocycle is 2-methoxy-5-ethyl-6-methyl-3-pyridyl,
2-benzoxazolyl, 7-methyl-2-benzoxazolyl,
25 4,7-dimethyl-2-benzoxazolyl, 7-chloro-2-benzoxazolyl,
or 4,7-dichloro-2-benzoxazolyl.

9. A compound, which is
3-[2-(4,7-dichlorobenzoxazol-2-yl)ethyl]-5-ethyl-
6-hydroxymethylpyridin-2(1H)-one,
3-[(4,7-dichlorobenzoxazol-2-yl)methylamino]-5-
5 ethyl-6-hydroxymethylpyridin-2(1H)-one,
3-{N-[(2-methoxy-5-ethyl-6-methylpyridin-3-yl)-
methy1]amino}-5-ethyl-6-hydroxymethylpyridin-2(1H)-
one,
3-[2-(4,7-Dichlorobenzoxazol-2-yl)ethyl]-5-ethyl-6-
10 hydroxymethylpyridin-2(1H)-thione,
3-[(4,7-Dichlorobenzoxazol-2-yl)methylamino-5-
[1(R,S)-hydroxyethyl]-6-methylpyridin-2(1H)-one,
3-[(4,7-Dichlorobenzoxazol-2-yl)methylamino-5-(1-
oxoethyl)-6-methylpyridin-2(1H)-one,
15 3-[(4,7-Dichlorobenzoxazol-2-yl)methylamino-5-[1-
(S,R)-hydroxyethyl]-6-methylpyridin-2(1H)-one,
3-[(5-Ethyl-2-methoxy-6-methylpyridin-3-yl)methyl]-
amino-5-[1(R,S)-hydroxyethyl]-6-methylpyridin-2(1H)-
one,
20 5-Ethyl-3-[2-(4-fluorobenzoxazol-2-yl)ethyl]-6-
hydroxymethylpyridin-2(1H)-one,
3-{N-[(5,6-Dimethyl-3-methoxypyridin-2-yl)methyl]-
amino}-5-ethyl-6-hydroxymethylpyridin-2(1H)-one,
5-Ethyl-6-hydroxymethyl-3-{N-[(3-methoxy-5,6,7,8-
25 tetrahydroquinolin-2-yl)methyl]amino}pyridin-2(1H)-
one,
5-Ethyl-3-{N-[(6-ethyl-3-methoxy-5-methylpyridin-2-
y1)methyl]amino}-6-hydroxymethylpyridin-2(1H)-one,
3-{N-[(5,6-dimethyl-2-methoxypyridin-3-yl)methyl]-
30 amino}-5-ethyl-6-hydroxymethylpyridin-2(1H)-one,

5-Ethyl-6-hydroxymethyl-3-{N-[*(2-methoxy-5,6,7,8-tetrahydroquinolin-3-yl)methyl*]amino}pyridin-2(1H)-one,
3-{N-[*(2-methoxy-5,6-trimethylene-pyridin-3-yl)methyl*]amino}-5-ethyl-6-hydroxymethylpyridin-2(1H)-one,
3-{N-[*(6-methoxy-indan-5-yl)methyl*]amino}-5-ethyl-6-hydroxymethylpyridin-2(1H)-one,
3-{N-[*(5-ethyl-2-methoxypyridin-3-yl)methyl*]amino}-5-ethyl-6-hydroxymethylpyridin-2(1H)-one,
5-Ethyl-6-hydroxymethyl-3-{N-[*(2-methoxyquinolin-3-yl)methyl*]amino}pyridin-2(1H)-one,
3-{N-[*(3-methoxy-5,6-trimethylene-pyridin-2-yl)methyl*]amino}-5-ethyl-6-hydroxymethylpyridin-2(1H)-one,
3-{N-[*(3-methoxy-5-ethylpyridin-2-yl)methyl*]amino}-5-ethyl-6-hydroxymethylpyridin-2(1H)-one,
3-[N-(5-ethyl-2-methoxybenzyl)amino]-5-ethyl-6-hydroxymethylpyridin-2(1H)-one,
3-[2-(4,7-difluorobenzoxazol-2-yl)ethyl]-5-ethyl-6-hydroxymethylpyridin-2(1H)-one, or
3-[N-(4,5-dimethyl-2-methoxybenzyl)amino]-5-ethyl-6-hydroxymethylpyridin-2(1H)-one,
25 or pharmaceutically acceptable salt or ester thereof.

10. A compound of the formula:

5

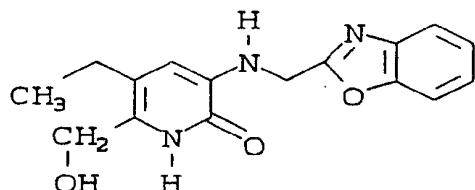


10

or pharmaceutically acceptable ester thereof.

11. A compound of the formula:

15

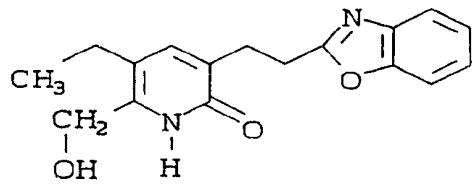


20

or pharmaceutically acceptable ester thereof.

12. A compound of the formula:

25



30

or pharmaceutically acceptable ester thereof.

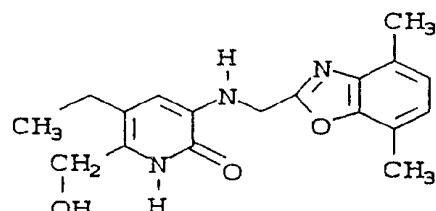
156 / RDM81

- 98 -

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13. A compound of the formula:

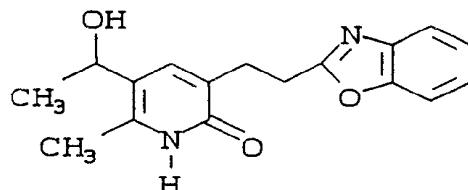
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10 or pharmaceutically acceptable ester thereof.

14. A compound of the formula:

15

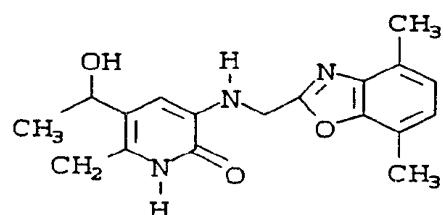


20

or pharmaceutically acceptable ester thereof.

15. A compound of the formula:

25

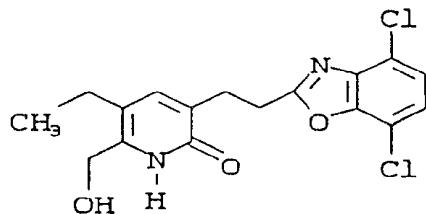


30

or pharmaceutically acceptable ester thereof.

16. A compound of the formula

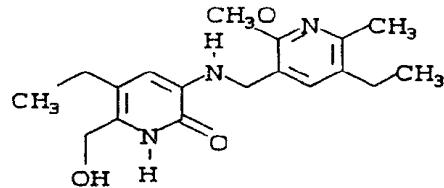
5



10 or pharmaceutically acceptable ester thereof.

17. A compound of the formula

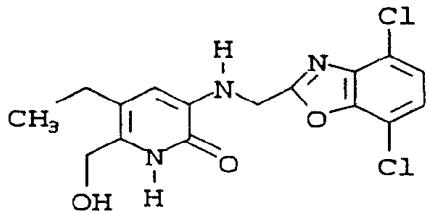
15



20 or pharmaceutically acceptable ester thereof.

18. A compound of the formula

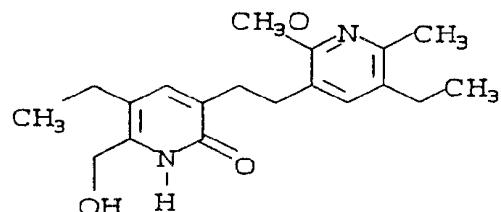
25



30 or pharmaceutically acceptable ester thereof.

19. A compound of the formula

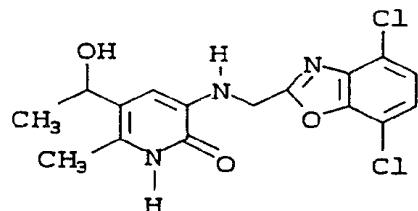
5



10 or pharmaceutically acceptable ester thereof.

20. A compound of the formula

15

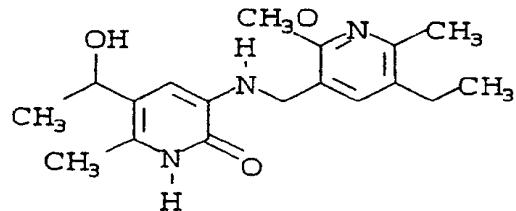


20

or pharmaceutically acceptable ester thereof.

21. A compound of the formula

25



30

or pharmaceutically acceptable ester thereof.

22. A method of preparing the compounds of
Claim 10 or 11, comprising the steps of:

5 (a) providing a quantity of 3-[(2-benzox-
azolyl-methyl)amino]-5-ethyl-6-methyl-2-
(1H)-pyridinone;

(b) incubating the sample of step (a) with
culture MA6559(ATCC 53771); and

(c) isolating the compound of Claim 10 or
11.

10

23. A method of inhibiting HIV reverse
transcriptase, comprising administering to a suitable
mammal in need of such treatment an effective amount
of a compound as in any of claims 1-21.

15

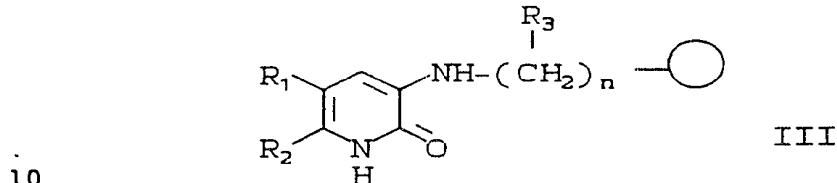
24. A method of preventing infection of
HIV, or of treating infection by HIV or of treating
AIDS or ARC, comprising administering to a suitable
mammal in need of such treatment an effective amount
20 of a compound as in any of claims 1-21.

25. A pharmaceutical composition useful for
inhibiting HIV reverse transcriptase, comprising an
effective amount of a compound as in any of claims
25 1-21 and a pharmaceutically acceptable carrier.

26. A pharmaceutical composition useful for
preventing or treating infection of HIV or for
treating AIDS or ARC, comprising an effective amount
30 of a compound as in any of claims 1-21, and a
pharmaceutically acceptable carrier.

27. A process for synthesizing a compound of formula III,

5



wherein

n is 1-4;

15 R₁ is (i) C₁₋₈ alkyl, unsubstituted or substituted with one or two of C₁₋₃alkoxy, halo, hydroxyl,

C₁₋₄alkylamino, C₁₋₄-di-(alkyl)amino, or C₁₋₃ alkylthio;

20 (ii) C₁₋₃ alkylthio;
(iii) C₁₋₃ alkoxy; or
(iv) halo;

25 R₂ is H, methyl or ethyl, unsubstituted or substituted with one or two of methoxy, hydroxyl, methylamino, dimethylamino or methylthio;
provided that one of R₁ or R₂, or both, is substituted at least once with hydroxyl;

R₃ is H or C₁₋₈ alkyl;

30

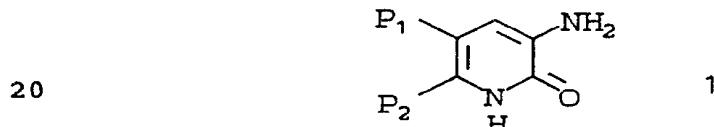


is aryl or heterocycle, each unsubstituted or substituted with one or more of

(a) C_{1-6} alkyl,
 (b) C_{1-6} alkoxy unsubstituted or
 substituted with hydroxy- C_{1-4} alkyl,
 (c) amino,
 5 (d) C_{1-6} alkyl amino,
 (e) di(C_{1-6} alkyl)amino,
 (f) amino- C_{1-8} alkyl,
 (g) C_{1-8} alkyl-amino- C_{1-8} alkyl,
 10 (h) di- $(C_{1-6}$ alkyl)amino C_{1-8} alkyl,
 (i) hydroxyl, or
 (j) halogen,

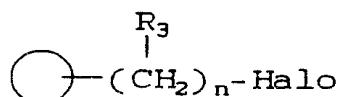
with the proviso that heterocycle is not phthalimide;

15 comprising the step of condensing



and

25

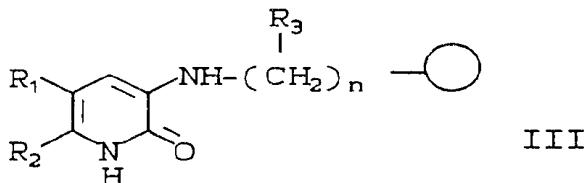


30

by alkylation in a process yielding a compound of
 Formula III.

28. A process for synthesizing a compound of Formula III,

5



10

wherein

n is 1-4;

R₁ is (i) C₁₋₈ alkyl, unsubstituted or substituted with one or two of C₁₋₃alkoxy, halo, hydroxyl, C₁₋₄alkylamino, C₁₋₄-di-(alkyl)amino, or C₁₋₃ alkylthio;

(ii) C₁₋₃ alkylthio;
 (iii) C₁₋₃ alkoxy; or
 (iv) halo;

R₂ is H, methyl or ethyl, unsubstituted or substituted with one or two of methoxy, hydroxyl, methylamino, dimethylamino or methylthio;

provided that one of R₁ or R₂, or both, is substituted at least once with hydroxyl;

R₃ is H or C₁₋₈ alkyl;

30



is aryl or heterocycle, each unsubstituted or substituted with one or more of

156/RDM81

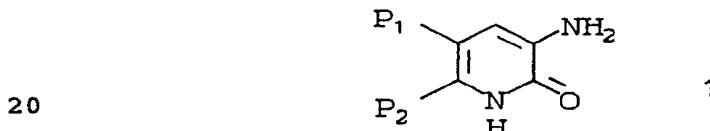
- 105 -

18212IB

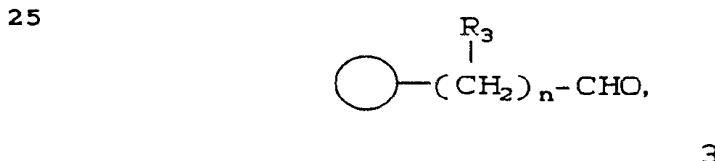
(a) C_{1-6} alkyl,
 (b) C_{1-6} alkoxy unsubstituted or
 substituted with hydroxy- C_{1-4} alkyl,
 (c) amino,
 5 (d) C_{1-6} alkyl amino,
 (e) di(C_{1-6} alkyl)amino,
 (f) amino- C_{1-8} alkyl,
 (g) C_{1-8} alkyl-amino- C_{1-8} alkyl,
 10 (h) di-(C_{1-6} alkyl)amino C_{1-8} alkyl,
 (i) hydroxyl, or
 (j) halogen,

with the proviso that heterocycle is not phthalimide;

15 comprising the step of condensing



and

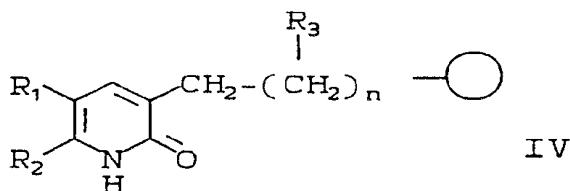


30

by reductive alkylation in a process yielding a compound of Formula III.

29. a process for synthesizing a compound of Formula IV,

5



10

wherein

n is 1-4;

R₁ is (i) C₁₋₈ alkyl, unsubstituted or substituted with one or two of C₁₋₃alkoxy, halo, hydroxyl,

C₁₋₄alkylamino, C₁₋₄-di-(alkyl)amino, or C₁₋₃ alkylthio;

(ii) C₁₋₃ alkylthio;
 (iii) C₁₋₃ alkoxy; or
 (iv) halo;

R₂ is H, methyl or ethyl, unsubstituted or substituted with one or two of methoxy, hydroxyl, methylamino, dimethylamino or methylthio;

provided that R₁ or R₂, or both, is substituted at least once with hydroxyl;

R₃ is H or C₁₋₈ alkyl;

30



is aryl or heterocycle, each unsubstituted or substituted with one or more of

156/RDM81

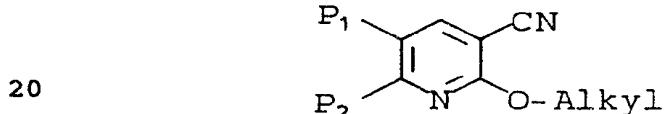
- 107 -

18212IB

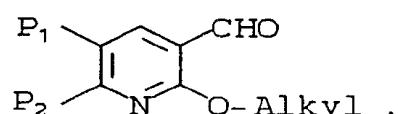
- (a) C_{1-6} alkyl,
- (b) C_{1-6} alkoxy unsubstituted or substituted with hydroxy- C_{1-4} alkyl,
- (c) amino,
- 5 (d) C_{1-6} alkyl amino,
- (e) di(C_{1-6} alkyl)amino,
- (f) amino- C_{1-8} alkyl,
- (g) C_{1-8} alkyl-amino- C_{1-8} alkyl,
- 10 (h) di- $(C_{1-6}$ alkyl)amino C_{1-8} alkyl,
- (i) hydroxyl, or
- (j) halogen,

with the proviso that heterocycle is not phthalimide;

15 comprising conversion of the intermediate



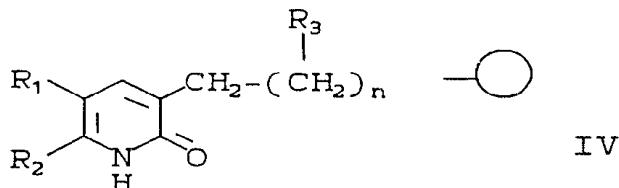
25 to the intermediate



30

30. A process for synthesizing a compound of Formula IV,

5



10

wherein

n is 1-4;

15

R₁ is (i) C₁₋₈ alkyl, unsubstituted or substituted with one or two of C₁₋₃alkoxy, halo, hydroxyl,

C₁₋₄alkylamino, C₁₋₄-di-(alkyl)amino, or C₁₋₃ alkylthio;

20

(ii) C₁₋₃ alkylthio;

(iii) C₁₋₃ alkoxy; or

(iv) halo;

R₂ is H, methyl or ethyl, unsubstituted or substituted with one or two of methoxy, amino, methylamino, dimethylamino or methylthio;

25

provided that one of R₁ or R₂, or both, is substituted at least once with hydroxyl;

R₃ is H or C₁₋₈ alkyl;

30

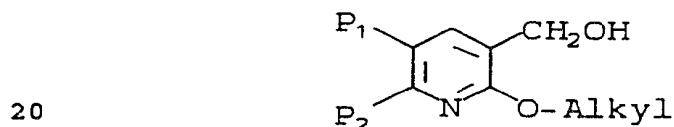


is aryl or heterocycle, each unsubstituted or substituted with one or more of

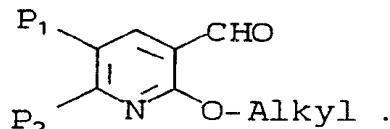
(a) C_{1-6} alkyl,
(b) C_{1-6} alkoxy unsubstituted or
substituted with hydroxy- C_{1-4} alkyl,
(c) amino,
5 (d) C_{1-6} alkyl amino,
(e) di(C_{1-6} alkyl)amino,
(f) amino- C_{1-8} alkyl,
(g) C_{1-8} alkyl-amino- C_{1-8} alkyl,
10 (h) di-(C_{1-6} alkyl)amino C_{1-8} alkyl,
(i) hydroxyl, or
(j) halogen,

with the proviso that heterocycle is not phthalimide;

15 comprising conversion of the intermediate



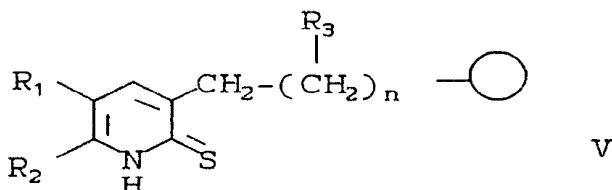
to the intermediate



30

31. A process for synthesizing a compound of formula V,

5



V

10

wherein

n is 1-4;

R₁ is (i) C₁₋₈ alkyl, unsubstituted or substituted with one or two of C₁₋₃alkoxy, halo, hydroxyl,

C₁₋₄alkylamino, C₁₋₄-di-(alkyl)amino, or C₁₋₃ alkylthio;

(ii) C₁₋₃ alkylthio;

(iii) C₁₋₃ alkoxy; or

(iv) halo;

R₂ is H, methyl or ethyl, unsubstituted or substituted with one or two of methoxy, hydroxyl, methylamino, dimethylamino or methylthio;

25 provided that one of R₁ or R₂, or both, is substituted at least once with hydroxyl;

R₃ is H or C₁₋₈ alkyl;

30

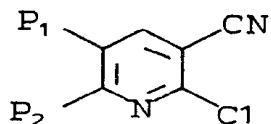


is aryl or heterocycle, each unsubstituted or substituted with one or more of

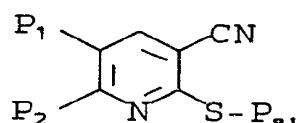
(a) C_{1-6} alkyl,
 (b) C_{1-6} alkoxy unsubstituted or
 substituted with hydroxy- C_{1-4} alkyl,
 (c) amino,
 5 (d) C_{1-6} alkyl amino,
 (e) di(C_{1-6} alkyl)amino,
 (f) amino- C_{1-8} alkyl,
 (g) C_{1-8} alkyl-amino- C_{1-8} alkyl,
 10 (h) di-(C_{1-6} alkyl)amino C_{1-8} alkyl,
 (i) hydroxyl, or
 (j) halogen,

with the proviso that heterocycle is not phthalimide;

15 comprising the step of thiolating



25 to yield



30 wherein P_s is a thio protecting group;

in a process yielding a compound of formula V.

32. A use of an effective amount of a compound as in any one of claims 1 to 21 for inhibiting HIV reverse transcriptase in a suitable mammal in need thereof.

33. A use of an effective amount of a compound as in any one of claims 1 to 21 for preventing infection of HIV or for treating infection by HIV or for treating AIDS or ARC in a suitable mammal in need thereof.

SUBSTITUTE
REPLACEMENT

SECTION is not Present
Cette Section est Absente